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(54) Title: MONOCLONAL ANTIBODIES WITH REDUCED IMMUNOGENICITY

(57) Abstract

Antibodies having reduced immunogenicity and methods for making them are disclosed.

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MONOCLONAL ANTIBODIES WITH REDUCED IMMUNOGENICITY

This application claims the benefit of U.S. Provisional Application No. 60/083,367, filed April 28, 1998.

Field of the Invention

This invention relates to monoclonal antibodies (mAbs) having reduced immunogenicity in humans.

Background of the Invention

Many potentially therapeutic mAbs are first generated in a murine hybridoma system for reasons of speed and simplicity. Non-human mAbs contain substantial stretches of amino acid sequences that will be immunogenic when injected into a human patient. It is well known that after injection of a foreign antibody, such as a murine antibody, a patient can have a strong human anti-mouse antibody (HAMA) response that essentially eliminates the antibody's therapeutic utility after the initial treatment as well as the utility of any other subsequently administered murine antibody.

Humanization techniques are well known for producing mAbs which exhibit reduced immunogenicity in humans while retaining the binding affinity of the original non-human parental mAb. See, *e.g.*, those disclosed in U.S. Patent Nos. 5,585,089; 5,693,761; 5,693,762; and 5,225,539.

In general, these methods depend on replacing human variable heavy and light region complementarity determining regions (CDRs) with antigen specific non-human CDRs, a process known as CDR grafting. It is also well known that in CDR grafting experiments the retention of the original antigen binding affinity is enhanced and in many cases depends on choosing human acceptor framework regions that most closely match the corresponding frameworks of the CDR donor antibody.

However, since the human genome contains a limited repertoire of heavy and light chain framework regions, these methods suffer from the limitation of available human acceptor frameworks. This restriction in acceptor framework repertoire necessarily can limit the degree of match between the non-human donor and the human acceptor antibody. Thus,

CDR grafting methods are limited by the known available repertoire of human VH and VL framework regions. Clearly, a need exists for an expanded range of acceptor V regions.

Summary of the Invention

One aspect of the present invention is an antibody comprising donor CDRs derived from an antigen-specific donor antibody of a non-human species and acceptor framework residues derived from a non-human primate.

Another aspect of the invention is a method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous non-human primate acceptor frameworks.

Another aspect of the invention is a chimpanzee VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17 or 18.

Another aspect of the invention is a chimpanzee VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 81, 82, 83, 84 or 85.

Another aspect of the invention is a chimpanzee Vκ acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 28, 29, 30, 31, 32, 33, 34, 35 or 36.

Another aspect of the invention is a chimpanzee Vκ acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 86 or 87.

Another aspect of the invention is a cynomolgus VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51 or 52.

Another aspect of the invention is a cynomolgus VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 88, 89, 90, 91, 92 or 93.

Another aspect of the invention is a cynomolgus Vκ acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 59, 60, 61, 62, 63 or 64.

Another aspect of the invention is a cynomolgus Vκ acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 94, 95 or 96.

Yet another aspect of the invention is an isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36.

Yet another aspect of the invention is an isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 81, 82, 83, 84, 85, 86 or 87.

Yet another aspect of the invention is an isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64.

Yet another aspect of the invention is an isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 88, 89, 90, 91, 92, 93, 94, 95 or 96.

Brief Description of the Drawings

Figure 1 is an amino acid sequence of the engineered 4A6 VL region. Asterisks above the 4A6 sequence indicate the 4A6 framework residues retained in the engineered molecule. Bold and italicized letters indicate the CDRs.

Figure 2 is an amino acid sequence of the engineered 4A6 VH region. Asterisks above the 4A6 sequence indicate the 4A6 framework residues retained in the engineered molecule. Bold and italicized letters indicate the CDRs.

Figure 3 is an amino acid sequence alignment comparing the murine antibody B9Vκ with the closest matching chimpanzee Vκ and selected Jκ sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. The numbering convention is from Kabat *et al., infra.*

Figure 4 is an amino acid sequence alignment comparing the murine antibody B9VH with the closest matching chimpanzee VH and selected JH sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat *et al., infra.*

Figure 5 is an amino acid sequence alignment comparing the murine antibody 3G9Vκ with the closest matching chimpanzee Vκ and selected Jk sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat *et al., infra*.

Figure 6 is an amino acid sequence alignment comparing the murine antibody 3G9VH with the closest matching chimpanzee VH and selected JH sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat *et al., infra*.

Detailed Description of the Invention

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

The molecular genetic aspects of antibody structure have been reviewed by S. Tonegawa in *Nature 302*:575-581 (1983). Briefly, antibodies are heterodimers comprised of at least two heavy and two light chains. The N-terminal domain of each heavy and light chain, termed VH and VL, respectively, fold together to form the antigen combining site. On the genetic level, the VL domain is encoded by two different gene segments, termed Vκ or Vl, and Jκ or Jl that join together to form one continuous VL region. Similarly, the VH domain is encoded by three gene segments, VH, DH, and JH, that join together to form one continuous VH region. Thus different VL and VH regions may be encoded by different combinations of Vκ or Vl, Jκ or Jl and VH, DH, and JH. This combinatorial diversity is in part the means by which the immune response generates the myriad diversity of different antibody molecules and their associated antigen specificities.

On the protein level, each heavy and light V region domain may be further divided into three CDRs. Three heavy

and three light chain CDRs fold together to form the antigen binding surface and part of the underlying support structures that are required to maintain the exact three-dimensional structure of the antigen combining site. Flanking each CDR are framework regions that in most cases do not directly interact with the specific antigen, but rather serve to form the scaffold which supports the antigen binding properties of the CDRs. Each heavy and light chain has four framework regions, three derived from the VH or VL gene segment, the fourth is derived from the JH, Jκ, or Jl gene segment. Thus, the order of frameworks and CDRs from the N- terminus is framework I, CDRI, framework II, CDRII, framework III, CDRIII, framework IV. On the genetic level, all of framework I through Framework III is encoded by the V region gene segment; CDRIII is encoded jointly by both the V region and J region gene segments; framework IV is encoded entirely from the J gene segment.

As used herein, "antibodies" refers to immunoglobulins and immunoglobulin fragments lacking all or part of an immunoglobulin constant region, *e.g.*, Fv, Fab, Fab' or $F(ab')_2$ and the like.

The term "donor antibody" refers to a monoclonal or recombinant antibody which contributes the nucleic acid sequences of its variable regions, CDRs or other functional fragments or analogs thereof to an engineered antibody, so as to provide the engineered antibody coding region and resulting expressed engineered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody.

The term "acceptor antibody" refers to monoclonal or recombinant antibodies heterologous to the donor antibody, which contributes all, or a portion, of the nucleic acid sequences encoding its heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions or V region subfamily consensus sequences to the engineered antibody.

A "functional fragment" is a partial heavy or light chain variable sequence (*e.g.*, minor deletions at the amino or carboxy terminus of the immunoglobulin variable region)

which retains the same antigen binding specificity and affinity as the antibody from which the fragment was derived.

An "analog" is an amino acid sequence modified by at least one amino acid, wherein said modification can be chemical or a substitution, which modification permits the amino acid sequence to retain the biological characteristics, *e.g.*, antigen specificity and high affinity, of the unmodified sequence.

Methods are provided for making engineered antibodies with reduced immunogenicity in humans and primates from non-human antibodies. CDRs from antigen-specific non-human antibodies, typically of rodent origin, are grafted onto homologous non-human primate acceptor frameworks. Preferably, the non-human primate acceptor frameworks are from Old World apes. Most preferably, the Old World ape acceptor framework is from *Pan troglodytes, Pan paniscus* or *Gorilla gorilla*. Particularly preferred is the chimpanzee *Pan troglodytes*. Also preferred are Old World monkey acceptor frameworks. Most preferably, the Old World monkey acceptor frameworks are from the genus *Macaca*. Particularly preferred is the cynomolgus monkey *Macaca cynomolgus*.

Particularly preferred chimpanzee (*Pan troglodytes)* heavy chain variable region frameworks (VH) are CPVH41-12 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 10 and the framework IV amino acid sequence shown in SEQ ID NO: 83; CPVH41-1 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 11 and the framework IV amino acid sequence shown in SEQ ID NO: 85; CPVH41-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 12; CPVH41-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 13; CPVH41-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 14, CPVH41-9 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 15 and the framework IV amino acid sequence shown in SEQ ID NO: 81; CPVH41-10 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 16 and the framework IV amino acid sequence shown in SEQ ID NO: 82; CPVH41-18 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 17; and CPVH41-19 having the framework I, II and III

amino acid sequence shown in SEQ ID NO: 18 and the framework IV amino acid sequence shown in SEQ ID NO: 84.

Particularly preferred chimpanzee (*Pan troglodytes*) light chain kappa variable region frameworks (Vκ) are CPVκ46-1 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 28; CPVκ46-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 29; CPVκ46-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 30; CPVκ46-5 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 31; CPVκ46-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 32 and the framework IV amino acid sequence shown in SEQ ID NO: 86; CPVκ46-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 33 and the framework IV amino acid sequence shown in SEQ ID NO: 87; CPVκ46-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 34; CPVκ46-11 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 35; and CPVκ46-14 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 36.

Particularly preferred cynomolgus (*Macaca cynomolgus*) heavy chain variable region frameworks (VH) are CYVH2-1 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 45 and the framework IV amino acid sequence shown in SEQ ID NO: 88; CYVH2-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 46 and the framework IV amino acid sequence shown in SEQ ID NO: 89; CYVH2-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 47 and the framework IV amino acid sequence shown in SEQ ID NO: 90; CYVH2-5 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 48 and the framework IV amino acid sequence shown in SEQ ID NO: 93; CYVH2-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 49 and the framework IV amino acid sequence shown in SEQ ID NO: 91; CYVH2-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 50; CYVH2-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 51; and CYVH2-10 having the

framework I, II and III amino acid sequence shown in SEQ ID NO: 52 and the framework IV amino acid sequence shown in SEQ ID NO: 92.

Particularly preferred cynomolgus (*Macaca cynomolgus*) light chain kappa variable region frameworks (Vκ) are CYVκ4-2 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 59; CYVκ4-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 60 and the framework IV amino acid sequence shown in SEQ ID NO: 94; CYVκ4-5 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 61; CYVκ4-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 62 and the framework IV amino acid sequence shown in SEQ ID NO: 95; CYVκ4-10 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 63; and CYVκ4-11 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 64 and the framework IV amino acid sequence shown in SEQ ID NO: 96.

Isolated nucleic acid molecules encoding the chimpanzee VH and Vκ acceptor framework I, II and III amino acid sequences of SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36 and the framework IV amino acid sequences of SEQ ID NOs: 81, 82, 83, 84 ,85, 86 or 87 are also part of the present invention. Further, isolated nucleic acid molecules encoding the cynomolgus VH and Vκ acceptor framework I, II and III amino acid sequences of SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64 and the framework IV amino acid sequences of SEQ ID NOs: 88, 89, 90, 91, 92, 93, 94, 95 or 96 are also part of the present invention. Nucleic acid sequences encoding functional fragments or analogs of the VH and Vκ acceptor framework amino acid sequences are also part of the present invention.

In addition to isolated nucleic acid sequences encoding VH and Vk acceptor frameworks described herein, nucleic acid sequences complementary to these framework regions are also encompassed by the present invention. Useful DNA sequences include those sequences which hybridize under stringent hybridization conditions to the DNA sequences. See, T.

Maniatis *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory (1982), pp. 387-389. An example of one such stringent hybridization condition is hybridization at 4XSSC at 65°C, followed by a washing in 0.1XSSC at 65°C for one hour. Alternatively, an exemplary stringent hybridization condition is 50% formamide, 4XSSC at 42°C. Preferably, these hybridizing DNA sequences are at least about 18 nucleotides in length.

Suitable frameworks are selected by computer homology searching among members of a database of Old World ape or monkey VH and VL regions. The framework portions of primate antibodies are useful as components of therapeutic antibodies. Moreover, primate antibody frameworks will be tolerated when used in the treatment of humans due to the close sequence homology between the genes of the primates and humans. Thus, the present invention provides for the grafting of CDRs from an antigen specific non-human donor antibody to acceptor V regions derived from non-human primate species.

The antigen specificity and binding kinetics of the donor antibody, which may be of rodent or any other non-human origin, are best preserved by selecting primate acceptor V regions that are determined by computer homology searching to be most similar to the donor antibody. Alternatively, the acceptor antibody may be a consensus sequence generated from primate V region subfamilies, or portions thereof, displaying the highest homology to the donor antibody.

The resulting engineered constructs, in which the donor CDRs are grafted onto primate acceptor frameworks, are subsequently refined by analysis of three-dimensional models based on known antibody crystal structures as found, *e.g.*, in the Protein Data Bank, http://www.pdb.bnl.gov/pdb-bin/pdbmain. Alternatively, computer generated three-dimensional models of the donor antibody may be computed by means of commercially available software such as "AbM" (Oxford Molecular, Oxford, UK).

Structural analysis of these models may reveal donor framework residues that are CDR-contacting residues and that are seen to be important in the presentation of CDR loops,

and therefore binding avidity. A CDR-contacting residue is one which is seen in three-dimensional models to come within the van der Waals radius of a CDR residue, or could interact with a CDR residue via a salt bridge or by hydrophobic interaction. Such donor framework (CDR-contacting) residues may be retained in the engineered construct.

The modeling experiments can also reveal which framework residues are largely exposed to the solvent environment. The engineered constructs may be further improved by substituting some or all of these solvent-accessible amino acid residues with those found at the same position among human V regions most homologous to the engineered construct as disclosed in U.S. Patent No. 5,639,641.

The engineered V regions are then joined to one or more different human or Old World ape constant regions depending on the desired secondary immune functions such as complement fixation or Fc receptor binding. Human constant regions can be selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. An IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function can also be selected. See U.S. Patent Nos. 5,624,821 and 5,648,260.

The complete heavy and light chain genes are transferred to suitable expression vectors and co-expressed in the appropriate host cells such as chinese hamster ovary, COS or myeloma cells. The resulting engineered antibody is expected to be of substantially reduced immunogenicity when administered to humans, and to retain full binding affinity for antigen.

Acceptor V regions can be isolated specifically for each donor V region by directed PCR methodology where a non-human primate cDNA library is surveyed for acceptor frameworks most similar to the donor antibody. Oligonucleotide PCR primers homologous to the donor antibody framework I (paired with C-region 3' PCR primers) are used to direct PCR amplification of a non-human primate, *e.g.*, chimpanzee lymphocyte cDNA library. This would select for V-regions with framework I regions similar to the donor antibody, and sequence analysis of the obtained clones would reveal the associated framework

II and III (and IV) sequences. 3' PCR primers would then be designed based on the knowledge of the non-human primate framework III sequences thus obtained, and used to direct PCR amplification of the original cDNA library together with a vector-specific 5' PCR primer. cDNA clones obtained from the second round of PCR amplification would have framework I and III sequences most similar to the donor antibody, and the framework II sequences would display a similar degree of sequence homology.

The present invention will now be described with reference to the following specific, non-limiting examples.

Example 1

Random cDNA Cloning and Sequence Analysis of Chimpanzee VH Regions

Five ml of peripheral blood was collected and pooled from three chimpanzees (*Pan troglodytes*) and peripheral blood mononuclear cells were isolated by standard density centrifugation methods. These cells, which include antibody producing lymphocytes, were dissolved in TRIzol reagent (GIBCO, Gaithersburg, MD, USA) and total RNA was recovered from this material by solvent extraction and precipitation according to the manufacturer's specifications.

Chimpanzee heavy chain V regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol using 3' Cg1 gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct heavy chain V region clones, nine were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the chimpanzee VH cDNA clones 41-12, 41-1, 41-4, 41-7, 41-8, 41-9, 41-10, 41-18 and 41-19 are shown in SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8 and 9, respectively. The amino acid sequences of the region from the first amino acid of the mature VH region to the second conserved cysteine residue at position 92, adjacent to CDR III of these clones, namely, CPVH41-12,

CPVH41-1, CPVH41-4, CPVH41-7, CPVH41-8, CPVH41-9, CPVH41-10, CPVH41-18 and CPVH41-19 are shown in SEQ ID NOs: 10, 11, 12, 13, 14 ,15, 16, 17 and 18, respectively. The amino acid sequence of the region encoding framework IV of these clones for CPVH41-9, CPVH41-10, CPVH41-12, CPVH41-19 and CPVH 41-1 are shown in SEQ ID NOs: 81, 82, 83, 84 and 85, respectively.

The chimpanzee VH amino acid sequences from the mature N-terminus and the second conserved cysteine residue at position 92, adjacent to CDRIII, were used as query sequences in computer homology searching of the Kabat database of Sequences of Proteins of Immunological Interest (ftp://ncbi.nlm.nih.gov/repository/kabat/) The results of this analysis are shown in Table 1.

In each case, the closest match was with a human VH region, displaying between 76% (41-1/HHC20G) and 94% (41-10/HHC20Y) sequence identity at the amino acid level. Matches were found for each of the three major human VH subgroups, indicating that the chimpanzee VH repertoire includes at least some members homologous to each of the major human subgroups. The human subgroup homology is presented in Table 1.

Table 1

Clone	Closest Match	Overall Amino Acid Homology	VH Subgroup Match
41-4	HHC10X	88%	I
41-9	HHC10Y	92	I
41-18	HHC10D	84	I
41-1	HHC20G	76	II
41-10	HHC20Y	94	II
41-12	HHC20C	83	II
41-7	HHC30T	80	III
41-8	HHC30T	79	III
41-19	HHC305	82	III

The results show that the overall sequence identity between the chimpanzee and human VH regions ranged between 76 and 95% with a mean identity of 84%. Based on this observation, further sampling of the chimpanzee random VH library will likely provide a substantially greater diversity of VH sequences from which to choose optimum acceptor frameworks for each particular donor VH region.

Example 2

Random cDNA Cloning and Sequence Analysis of Chimpanzee Vκ Regions

Chimpanzee light chain Vκ regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol and Cκ 3' gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct light chain Vκ region clones, nine were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the chimpanzee Vκ cDNA clones 46-1, 46-3, 46-4, 46-5, 46-6, 46-7, 46-8, 46-11 and 46-14 are shown in SEQ ID NOs: 19, 20, 21, 22, 23, 24, 25, 26 and 27, respectively. The amino acid sequences of the region from the first amino acid of the mature Vκ region to the second conserved cysteine residue at position 88, adjacent to CDR III of these clones, namely CPVκ46-1, CPVκ46-3, CPVκ46-4, CPVκ46-5, CPVκ46-6, CPVκ46-7, CPVκ46-8, CPVκ46-11 and CPVκ46-14 are shown in SEQ ID NOs: 28, 29, 30, 31, 32, 33, 34, 35 and 36, respectively. The amino acid sequences of the region encoding framework IV of these clones for CPVκ46-6 and CPVκ46-7 are shown in SEQ ID NOs: 86 and 87, respectively.

The chimpanzee Vκ amino acid sequences comprising the mature N-terminus and the second conserved cysteine residue at position 88 were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 2. In each case the closest match was with a human Vκ region, displaying between 68% (46-4/HKL310) and 97% (46-11/HKL106) sequence identity at the amino acid level. It is evident that the chimpanzee Vκ sequences are distinct from the collection of human Vκ found in the Kabat database.

The human subgroup homology is presented in Table 2. Of the four major human Vκ subgroups, matches were found for the two most frequently isolated, indicating that the chimpanzee Vκ repertoire is at least homologous to members of the majority of the human Vκ repertoire. Further sampling of the chimpanzee Vκ cDNA library will likely identify a greater diversity of chimpanzee Vκ regions, including ones homologous to the remaining two human Vκ subgroups (VκII and VκIV).

Table 2

Clone	Closest Match	Overall Amino Acid Homology	VH Subgroup Match
46-1	HKL10C	85%	I
46-3	HKL 10O	91	I
46-5	HKL 10O	91	I
46-7	HKL 10O	81	I
46-8	HKL 10N	90	I
46-11	HKL 106	97	I
46-14	HKL 10O	92	I
46-4	HKL 310	68	III
46-6	HKL 310	96	III

Example 3

Random cDNA Cloning and Sequence Analysis of Cynomolgus VH Regions

Splenic RNA was recovered from a single donor cynomolgus monkey (*Macaca cynomolgus*) by means of standard laboratory practice. Cynomolgus heavy chain V regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol using 3' Cg1 gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct heavy V region clones, eight were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the Cynomolgus VH cDNA clones 2-1, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8 and 2-10 are shown in SEQ ID NOs: 37, 38, 39, 40, 41, 42, 43 and 44, respectively. The amino acid sequences of the region from the first amino acid of the mature VH region to the second conserved cysteine residue at position 92, adjacent to CDR III of these clones, namely CyVH2-1, CyVH2-3, CyVH2-4, CyVH2-5, CyVH2-6, CyVH2-7, CyVH2-8 and CyVH2-10 are shown in SEQ ID NOs: 45, 46, 47, 48,

49, 50, 51 and 52, respectively. The amino acid sequences of the region encoding framework IV of these clones for CyVH2-1, CyVH2-3, CyVH2-4, CyVH2-6, CyVH2-10 and CyVH2-5 are shown in SEQ ID NOs: 88, 89, 90, 91, 92 and 93, respectively.

The cynomolgus VH amino acid sequences from the mature N-terminus and the second conserved cysteine residue at position 92, adjacent to CDRIII, were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 3. In each case the closest match was with a human VH region, displaying between 62% (2-6/ HHC20E) and 84% (2-5/ HHC20F) sequence identity at the amino acid level. It is evident that the cynomolgus VH sequences are distinct from the collection of human VH found in the Kabat database. Matches were found for each of the three major human VH subgroups, indicating that the cynomolgus VH repertoire includes at least some members homologous to each of the major human subgroups. The human subgroup homology is presented in Table 3.

Table 3

Clone	Closest Match	Overall Amino Acid Homology	VH Subgroup Match
2-4	HHC10Y	83%	I
2-10	HHC20G	83	II
2-8	HHC20F	74	II
2-6	HHC20E	62	II
2-5	HHC20F	84	II
2-3	HHC20F	75	II
2-1	HHC316	71	III
2-7	HHC31C	81	III

The results show that the overall sequence identity between the cynomolgus and human VH regions ranged between 62 and 84% with a mean identity of 77%. Based on this observation, further sampling of the cynomolgus random VH library will likely provide a substantially greater diversity of VH sequences from which to choose optimum acceptor frameworks for each particular donor VH region.

Example 4

Random cDNA Cloning and Sequence Analysis of Cynomolgus Vκ Regions

Cynomolgus light chain Vκ regions were cloned from the total splenic RNA using Marathon RACE methodology (Clontech,

Palo Alto, CA, USA) following exactly the manufacturer's protocol and Cκ 3' gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct light chain Vκ region clones, six were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the Cynomolgus Vκ cDNA clones 4-2, 4-3, 4-5, 4-6, 4-10 and 4-11 are shown in SEQ ID NOs: 53, 54, 55, 56, 57 and 58, respectively. The amino acid sequences of the region from the first amino acid of the mature Vκ region to the second conserved cysteine residue at position 88, adjacent to CDRIII, of these clones, namely CyVκ4-2, CyVκ4-3, CyVκ4-5, CyVκ4-6, CyVκ4-10 and CyVκ4-11 are shown in SEQ ID NOs: 59, 60, 61, 62, 63 and 64, respectively. The amino acid sequences encoding the framework IV region of these clones for CyVκ4-3, CyVκ4-6 and CyVκ4-11 are shown in SEQ ID NOs: 94, 95 and 96, respectively.

The cynomolgus Vκ amino acid sequences comprising the mature N-terminus and the second conserved cysteine residue at position 88 were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 4. In each case the closest match was with a human Vκ region, displaying between 73% (4-11/ HKL10S) and 94% (4-3/ HKL400) sequence identity at the amino acid level. It is evident that the cynomolgus Vκ sequences are distinct from the collection of human Vκ found in the public genetic databases. The human subgroup homology is presented in Table 4. Matches were found for three of the four major human Vk subgroups, indicating that the cynomolgus Vκ repertoire is largely homologous to members of the majority of the human Vκ repertoire. Further sampling of the cynomolgus Vκ cDNA library will likely identify a greater diversity of cynomolgus Vκ regions, including ones homologous to the remaining human Vκ subgroup (VκIII).

Table 4

Clone	Closest Match	Overall Amino Acid Homology	Vκ Subgroup Match
4-6	HKL10L	80%	I
4-2	HKL10Z	83	I
4-11	HKL10S	73	I
4-10	HKL10F	93	I
4-5	HKL209	86	II
4-3	HKL400	94	IV

The results show that the overall sequence identity between the cynomolgus and human Vκ regions ranged between 73 and 94% with a mean identity of 85%. Based on this observation, further sampling of the cynomolgus random Vκ library will provide a substantially greater diversity of Vκ sequences from which to choose optimum acceptor frameworks for each particular donor Vκ region.

Example 5

Preparation of Engineered Anti-IL-5 Monoclonal Antibodies

The Vκ and VH genes of the rat anti-interleukin-5 (IL-5) antibody 4A6 are shown in SEQ ID NOs: 65 and 66, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human IL-5 useful for the treatment of asthma. See U.S. Patent No. 5,693,323.

The 4A6 light chain was engineered as follows. The sequence of donor antibody Vκ4A6 (SEQ ID NO: 65) was aligned with the acceptor antibody light chain Vκ region from the chimpanzee Mab C108G (*Mol. Immunol. 32*:1081-1092 (1995)) (SEQ ID NO: 67) as shown in Fig. 1. Since native Vκ4A6 has a unique deletion of residue 10, the sequence alignment included the insertion of a gap at that position. The CDR residues were identified as defined by the convention of Kabat *et al.* in *Sequences of Proteins of Immunological Interest,* 4th ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this

CDR-contacting set were compared among the aligned Vκ4A6 and VκC108G sequences, and the positions of the set that differed between the Vκ4A6 and the VκC108G were marked (Fig. 1, asterisks). The CDRs and the marked framework residues of Vκ4A6 (the donor antibody) were transferred replacing the corresponding residues of VκC108G (the acceptor antibody). The completed engineered 4A6 light chain V region is shown in SEQ ID NO: 68. Six donor framework residues were retained in the engineered molecule at residues 1 to 4, 49 and 60.

In analogous fashion, a similar method was used to engineer the 4A6 heavy chain. The sequence of donor antibody VH4A6 (SEQ ID NO: 66) was aligned with the acceptor antibody heavy chain V region from the chimpanzee Mab C108G (SEQ ID NO: 69) as shown in Fig. 2. A large gap was introduced in the VH4A6 CDRIII alignment, as CDRIII of VHC108G is 10 residues longer. CDR residues were identified as defined by the convention of Kabat *et al.*, *supra.*

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VH4A6 and VHC108G sequences, and the positions of the set that differed between the VH4A6 and the VHC108G were marked (Fig. 2, asterisks). In total, 11 such CDR contacting residues that differed between VH4A6 and the VHC108G were selected and marked. The CDRs and the marked CDR contacting framework residues of VH4A6 (the donor antibody) were transferred replacing the corresponding residues of VHC108G (the acceptor antibody). The completed engineered 4A6 heavy chain V region is shown in SEQ ID NO: 70. Eleven donor framework residues were retained in the engineered molecule at residues 27, 30, 38, 49, 66, 67, 69, 71, 73, 78 and 94.

The engineered 4A6 can be expressed in cells using methods well known to those skilled in the art. Briefly, genes encoding the complete engineered 4A6 VH and Vκ regions can be assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing the desired antibody constant regions. Such an expression vector will contain selectable markers, for

example, neomycin resistance and regulatory sequences, for example, the CMV promoter, required to direct the expression of full-length antibody heavy and light chains. Subsequently, transfection of the appropriate host cell, for example, chinese hamster ovary, would result in the expression of fully active engineered 4A6.

Example 6

Preparation of Engineered Anti-Integrin Monoclonal Antibodies

The Vκ and VH genes of the murine anti-integrin antibody B9 are shown in SEQ ID NOs: 71 and 72, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human integrin αvβ3 useful for the treatment of vascular diseases.

The B9 light chain was engineered as follows. The amino acid sequence of donor antibody VκB9 (SEQ ID NO: 72) was compared to each of the nine chimpanzee Vκ sequences described above and percent sequence identity determined by computer homology searching using the LASERGENE program "MEGALIGN" (DNASTAR, Inc., Madison, WI). Clones CPVκ46-3 (SEQ ID NO: 29) and CPVκ46-14 (SEQ ID NO: 36) were identified as the chimpanzee Vκ regions with the highest overall sequence similarity (77%) to the B9 donor Vκ. CPVκ46-3 was selected as the acceptor framework.

Similarly, the chimpanzee Jκ gene segment of CPVκ46-1 (SEQ ID NO: 97) was selected as acceptor framework IV. The sequences of the donor VκB9 and acceptor CPVκ46-3, CPVκ46-1 V regions were aligned and the positions of their respective framework and CDRs were determined as shown in Fig. 3.

The CDR residues were identified as defined by the convention of Kabat *et al.*, *supra*. The results show that VκB9 and CPVκ46-3 share 77% overall sequence identity, with the framework regions I through III sharing 81% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this

CDR-contacting set were compared among the aligned VkB9 and CPVk46-3 sequences, and none of this set were found that differed between the VkB9 and the CPVk46-3. Accordingly, only the CDRs of VkB9 (the donor antibody) were transferred replacing the corresponding residues of CPVk46-3 (the acceptor antibody). Lastly, the framework IV sequences of CPVk46-1 replaced the corresponding framework IV residues of the B9 light chain variable region. The completed engineered B9 light chain V region is shown in SEQ ID NO: 73. No donor framework residues were retained in the engineered light chain variable region.

The B9 heavy chain was engineered in analogous fashion. The amino acid sequence of donor antibody VHB9 (SEQ ID NO: 71) was compared to each of the nine chimpanzee VH sequences described above by computer homology searching. Clone CPVH41-18 (SEQ ID NO: 17) was identified as the chimpanzee VH region with the highest overall sequence similarity (58%) to the B9 donor VH.

The chimpanzee JH gene segment of CPVH41-10 (SEQ ID NO: 82) was selected as acceptor framework IV. The sequences of the donor VHB9 and chimpanzee acceptor V regions were aligned and the positions of their respective framework and CDRs determined as shown in Fig. 4.

The CDR residues were identified as defined by the convention of Kabat *et al., supra*. The results show that VHB9 and CPVH41-18 share 58% overall sequence identity, with the framework regions I through III sharing 65% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VHB9 and CPVH41-18 sequences, and the nine residues of the set that differed between VHB9 and the chimpanzee acceptor frameworks were marked. The CDRs and the marked framework residues of donor antibody VHB9 were transferred replacing the corresponding residues of CPVH41-18 (the acceptor antibody). Lastly, the framework IV sequences of CPVH41-10 replaced the corresponding framework IV residues of the B9 heavy chain variable region. The completed engineered B9 heavy chain V

region is shown in SEQ ID NO: 74. Nine donor framework residues were retained in the engineered heavy chain variable region at positions 24, 27, 38, 48, 66, 67, 69, 93 and 94.

Example 7

Expression and Characterization of Engineered Anti-Integrin Monoclonal Antibodies

The engineered B9 antibody was expressed in cells using methods well known to those skilled in the art. Briefly, genes encoding the complete engineered B9 VH and Vκ regions were assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing IgG1,κ antibody constant regions. The expression vector contained a selectable marker for neomycin resistance and CMV promoter regulatory sequences. Subsequent transfection of a COS host cell resulted in the expression of engineered B9 (CPB9).

The relative binding avidity of CPB9 was compared to that of the original murine B9 antibody as follows. CPB9 antibodies present in culture supernatants from cells maintained in culture for 5 days after transfection with the expression constructs were compared to the parental murine B9 antibody using the ORIGEN technology (IGEN Inc, Gaithersburg, MD). Briefly, different dilutions of the B9 variants were incubated with purified human αvβ3 integrin which had previously been biotinylated, and an electrochemiluminescent TAG moiety specific for the antibody C regions. B9 variant antibody bound to the integrin was measured by capturing the immune complexes onto streptavidin beads followed by analysis on the ORIGEN instrument. The results showed that the CPB9 and the murine B9 binding curves were displaced only by about 3-fold indicating that the overall specific binding avidity of CPB9 and murine B9 for αvβ3 are within three-fold of each other. Accordingly, the results show that the CDR grafting of rodent CDRs onto chimpanzee frameworks as described in the present invention retained nearly all of the binding avidity of the parent rodent mAb.

Example 8

Preparation of Engineered Anti-Erythropoietin Receptor Monoclonal Antibodies

The VH and Vκ genes of the murine anti-erythropoietin receptor antibody 3G9 are shown in SEQ ID NOs: 75 and 76, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human erythropoietin receptor (EPOr) useful for the treatment of hematopoietic disorders.

The 3G9 light chain was engineered as follows. The amino acid sequence of donor antibody Vκ3G9 (SEQ ID NO: 76) was compared to each of the nine chimpanzee Vκ sequences described above by computer homology searching as described above. Clones CPVκ46-3 (SEQ ID NO: 29), CPVκ46-5 (SEQ ID NO: 31), CPVκ46-8 (SEQ ID NO: 34) and CPVκ46-14 (SEQ ID NO: 36) were identified as the chimpanzee Vκ regions with the highest overall sequence similarity (65%) to the 3G9 donor Vκ. CPVκ46-14 was selected as the acceptor framework.

The chimpanzee Jκ gene segment of CPVκ46-14 was identical to that of CPVκ46-1 (SEQ ID NO: 97) and was selected as acceptor framework IV. The sequences of the donor Vκ3G9 and acceptor CPVκ46-14 V regions were aligned and the positions of their respective framework and CDRs were determined as shown in Fig. 5.

The CDR residues were identified as defined by the convention of Kabat *et al.*, *supra*. The results show that Vκ3G9 and CPVκ46-14 share 65% overall sequence identity, with the framework regions I through III sharing 73% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned Vκ3G9 and CPVκ46-14 sequences, and the positions of this set that differed between Vκ3G9 and the CPVκ46-3 were marked. The CDRs and marked residues of Vκ3G9 (the donor antibody) were

transferred replacing the corresponding residues of CPVκ46-14 (the acceptor antibody). Lastly, the framework IV sequences of CPVκ46-14 replaced the corresponding framework IV residues of the 3G9 light chain variable region. The completed engineered 3G9 light chain V region is shown in SEQ ID NO: 77. Three donor framework residues were retained in the engineered light chain variable region at positions 3, 46 and 60.

The 3G9 heavy chain was engineered in analogous fashion. The amino acid sequence of donor antibody VH3G9 (SEQ ID NO: 75) was compared to each of the 9 chimpanzee VH sequences described above by computer homology searching. Clone CPVH41-18 (SEQ ID NO: 17) was identified as the chimpanzee VH region with the highest overall sequence similarity (53%) to the 3G9 donor VH.

The chimpanzee JH gene segment of CPVH41-18 was identical to CPVH41-9 (SEQ ID NO: 81) and was selected as acceptor framework IV. The sequences of the donor VH3G9 and chimpanzee acceptor V regions were aligned and the positions of their respective framework and CDRs determined as shown in Fig. 6.

The CDR residues were identified as defined by the convention of Kabat *et al.*, *supra*. The results show that VH3G9 and CPVH41-18 share 53% overall sequence identity, with the framework regions I through III sharing 62% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VH3G9 and CPVH41-18 sequences, and the twelve residues of the set that differed between VH3G9 and the chimpanzee acceptor frameworks were marked. The CDRs and the marked framework residues of donor antibody VH3G9 were transferred replacing the corresponding residues of CPVH41-18 (the acceptor antibody). Lastly, the framework IV sequences of CPVH41-18 replaced the corresponding framework IV residues of the 3G9 heavy chain variable region. The completed engineered 3G9 heavy chain V region is shown in SEQ ID NO: 78. Twelve donor framework residues were retained in the engineered heavy chain variable

region at positions 24, 27, 30, 38, 48, 66-69, 71, 73, and 94.

Example 9

Expression and Characterization of Engineered anti-Erythropoietin Receptor Monoclonal Antibodies

The engineered 3G9 antibody was expressed in cells using methods well known to those skilled in the art. Briefly, genes encoding the complete engineered 3G9 VH and Vκ regions were assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing IgG1,κ antibody constant regions. The expression vector contained a selectable marker for neomycin resistance and CMV promoter regulatory sequences. Subsequent transfection of COS host cells resulted in the expression of engineered 3G9 (CP3G9).

Culture supernatants from COS cells transiently transfected with chimpanzee framework engineered 3G9 were compared with another 3G9 variant for the ability to bind human EPOr. The entire extracellular domain of the EPOr was expressed as recombinant protein, purified, and adsorbed onto the wells of ELISA plates. Dilutions of different antibodies were then tested for the ability to specifically bind to the solid phase associated EPOr.

HZ3G9 is a humanized variant of 3G9 in which human frameworks were used in traditional CDR grafting experiments. The humanized 3G9 heavy chain amino acid sequence is shown in SEQ ID NO: 79. The humanized 3G9 light chain sequence is shown in SEQ ID NO: 80. Previous experiments showed that HZ3G9 retained the full binding affinity and avidity of the parental murine 3G9. Accordingly, since HZ3G9G1 is identical to the chimpanzee version in all respects except the V region cassette, it was used in the present comparative binding experiments as a surrogate for murine 3G9. Negative control antibodies were also tested, including HZD12 which is a humanized antibody specific for human integrin, and CPB9 which is a chimpanzee framework engineered antibody specific for human integrins described above. Different concentrations of the 3G9 variants and control antibodies were incubated for one hour. After washing, the bound

antibodies were detected by incubation with anti-human H+L antibody-enzyme conjugate, a final wash, and addition of chromagen.

The binding curves obtained for CP3G9 and HZ3G9 were superimposable. This result indicates that the human and the chimpanzee framework engineered versions of 3G9 have identical overall binding avidity for the specific antigen human EPOr. Since the constant regions of HZ3G9 and CP3G9 are identical, the results also suggest the full binding affinity of the original rodent 3G9 is retained in the chimpanzee version of 3G9. Accordingly, the results show that CDR grafting of rodent CDRs onto chimpanzee acceptor frameworks as described in the present invention retained the full binding avidity of the parental rodent antibody.

A BIAcore analysis (Pharmacia) was performed to determine the binding affinity for human EPOr of murine 3G9 and CP3G9. The interaction of CP3G9 as well as murine 3G9 with EPOr was characterized using a BIAcore 1000 biosensor. Descriptions of the instrumentation and the sensor surfaces are described in Brigham-Burke *et al., Anal. Biochem., 205*:125-131 (1992).

CP3G9 was captured onto a sensor surface of immobilized protein A. The kinetic binding constants were determined by passing solutions of monomeric EPOr over the surface and monitoring binding versus time. The equilibrium dissociation constant for the interaction was then derived from the ratio of the kinetic constants. The parent murine 3G9 was captured onto a surface of protein A captured rabbit anti-mouse Fc specific polyclonal antibody. The kinetics and dissociation constant for the interaction with EPOr was determined as described above. All measurements were made in 10 mM sodium phosphate, 150 mM NaCl pH 7.2 3 mM EDTA and 0.005% Tween 20. The flow rate was 60 uL/min. The temperature was 20° C.

	k_{ass} ($M^{-1}s^{-1}$)	k_{diss} (s^{-1})	K_D (nM)
murine 3G9	1.2×10^6	4.0×10^{-3}	3.3
CP3G9	1.0×10^6	9.1×10^{-3}	9.1

These results show that the dissociation equilibrium constants determined for the murine and chimpanzee framework versions of 3G9 are within three fold of each other. This

data is in good agreement with the results of the ELISA-based study described above. Accordingly, the results show that the process used in generating the chimpanzee version of 3G9 largely retained the binding affinity of the original rodent mAb.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof, and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

Claims

1. An antibody comprising donor CDRs derived from an antigen-specific donor antibody of a non-human species and acceptor framework residues derived from a non-human primate.

2. The antibody of claim 1 wherein the non-human primate is an Old World ape.

3. The antibody of claim 2 wherein the Old World ape is *Pan troglodytes, Pan paniscus* or *Gorilla gorilla*.

4. The antibody of claim 3 wherein the Old World ape is *Pan troglodytes*.

5. The antibody of claim 1 further comprising one or more CDR-contacting residues of the donor antibody.

6. The antibody of claim 1 comprising human or Old World ape constant regions.

7. The antibody of claim 1 wherein one or more solvent-exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate framework.

8. The antibody of claim 1 wherein the non-human primate is an Old World monkey.

9. The antibody of claim 8 wherein the Old World monkey genus is *Macaca*.

10. The antibody of claim 9 wherein the Old World monkey is *Macaca cynomolgus*.

11. The antibody of claim 8 further comprising one or more CDR-contacting residues of the donor antibody.

12. The antibody of claim 8 comprising human or Old World ape constant regions.

13. The antibody of claim 8 wherein one or more solvent-exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate framework.

14. A method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous Old World ape acceptor frameworks.

15. The method of claim 14 wherein the Old World ape acceptor framework is from *Pan troglodytes, Pan paniscus* or *Gorilla gorilla*.

16. The method of claim 15 wherein the Old World ape acceptor framework is from *Pan troglodytes*.

17. A method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous Old World monkey acceptor frameworks.

18. The method of claim 17 wherein the Old World monkey acceptor framework is from the genus *Macaca*.

19. The method of claim 18 whereiin the Old World Monkey acceptor framework is from *Macaca cynomolgus*.

20. A chimpanzee VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17 or 18.

21. A chimpanzee VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 81, 82, 83, 84 or 85.

22. A chimpanzee Vκ acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 28, 29, 30, 31, 32, 33, 34, 35 or 36.

23. A chimpanzee Vκ acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 86 or 87.

24. A cynomolgus VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51 or 52.

25. A cynomolgus VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 88, 89, 90, 91, 92 or 93.

26. A cynomolgus Vκ acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 59, 60, 61, 62, 63 or 64.

27. A cynomolgus Vκ acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 94, 95 or 96.

28. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36.

29. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 81, 82, 83, 84, 85, 86 or 87.

30. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64.

31. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 88, 89, 90, 91, 92, 93, 94, 95 or 96.

Figure 1

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        ****
4A6     DTVLTQSPA. LAVPPGERVT VSCRASESVS TFLHWYQQKP GHQP
C108G   AVHMTQSPSS LSASVGDSVT ITCRASQTIN IYLNWYQQKP GKAP
            *           *
4A6     KLLIYLASKL ESGVPARFSG GGSGTDFTLT IDPVEADDTA TYYCQQTWND
C108G   KLLIFDASIL QSGVPSRFSG SGSGTDFSLT IRSLQPEDFA TYYCQCGWGTH

4A6     PRTFGGGT KLELKR
C108G   PYNFGQGT KLEIKR
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Figure 2

* * *

4A6 EVQLQQSGPE VGRPGSSVKI SCKASGYTFT ***DYVLN***WVK QSPGQGLEWI
C108G EVQLVESGGG VVQPGGSLRL SCAASGFTFD ***DFAMH***WVR QAPGKGLEWI

* ** * * * *

4A6 G***WIDPDYG TTDYAEKFKK*** KATLTADTSS STAYIQLSSL TSEDTATYFC
C108G S***LVSWDSY NIYHADSVKG*** RFTISRDNSR NSLYLQMNDL RPEDTAIYFC

*

4A6 AR***SRNYGG***.. ....***YI NY***WGQGVMVTVS
C108G AK***ADTGGDFD YVSDSWRCAL DY***WGQGTLVTVS

Figure 3

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                1                                        CDR1
VLB9            DIQMTQTTSS LSASLGDRVT ITCRSSQ.......DISNFLN WYQQKPDGTV
Cmp46-3         DIQMTQSPSS LSASVGDRVT ITCRASQ.......GISNYLA WYQQKPGKAP

               45    CDR2                                          CDR3 94
VLB9            KLLIYYTSTL HSGVPSRFSG SGSGTDYSLT ISNLEQEDIA TYFCQQGNTL
Cmp46-3         KLLIYYASRL ESGVPSRFSG SGSGTDYTLT ISSLQPEDFA TYYCQQYNSN

               95
VLB9            P..WTFGGGT NLEIKR
cmp46-1              FGGGT KVEIKR
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Figure 4

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           1          11          21         CDR1      39        48
                                     *  *             *          *
VHB9       QVQLQQSGAE LMKPGASVKI SCKATGYTFS SYWIE..WVK QRPGHGLEWI
AMP41CL18  QVQLVQSGAE VKKPGSSVKV SCKVSGGTFS TYGFS..WVR QAPGQGLEWM

          49         CDR2       66         76         83        92
                                 ** *
VHB9       GEILP..RSG NTNYNEKFKG KATFTAETSS NTAYMQLSSL TPEDSAVYYC
AMP41CL18  GMIIP..IVG TVKYAQRFQG RVSINADTST NIAYMELTSL
RSEDTAVYYC

          93   CDR3            104
           **
VHB9       SSRGVRGSM.........DYW GQGTSVTVSS
AMP41CL18  ATDLTVTTNDAF......DI
AMP41CL10                     W GQGTLVTVSS
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Figure 5

```
             1                                    CDR1
              *
VL3G9        DIVMTQSQKF MSTSVGDRVS VTCKASQ.......NVGTNVA WYQQKPGQSP
VK46-14      DIQMTQSPSS LSASVGDRVT ITCRASQ.......SISNYLS WYQQKPGKAP

             45    CDR2                                          CDR3 94
              *              *
VL3G9        KALIYSASYR YSGVPDRFTG SGSGTDFTLT ISNVQSEDLA EYFCQQYNSY
VK46-14      KLLIYYASTL QSGVPSRFSG SGSGTDFTLT ISSLQPEDFA TYYCQHGYGT

                95
VL3G9        P..LTFGAGT KLELK
VK46-14      H..PTFGGGT KVEIK
```

Figure 6

```
           1          11         21         CDR1      39        48
                                     *  *  *           *          *
VH3G9      QVQLQQPGAE LVKSGASVKL SCKASGSTFT SYWMH..WVK QRPGRGLEWI
Chimp41-18 QVQLVQSGAE VKKPGSSVKV SCKVSGGTFS TYGFS..WVR QAPGQGLEWM

          49          CDR2       66         76         83       92
                                 **** * *
VH3G9      GRIDP..NSG GTKDNEKFKS KATLTVDKPS STAYMQLSSL TSEDSAVYYC
Chimp41-18 GMIIP..IVG TVKYAQRFQG RVSINADTST NIAYMELTSL RSEDTAVYYC

          93    CDR3             104
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VH3G9      ARETYYDSS. ......FAYW GQGTLVTVS
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SEQUENCE LISTING

<110> Taylor, Alexander H

<120> Monoclonal Antibodies with Reduced Immunogenicity

<130> P50770

<150> 60/083,367
<151> 1998-04-28

<160> 97

<170> FastSEQ for Windows Version 3.0

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Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1               5                  10                  15

gtc ctg tcc cag gtg cag ttg cag gag tcg ggc cca gga ctg gtg aag      96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

cct tca cag acc ttg tcc ctg acc tgc gct gtg tct ggt ggc tcc atc     144
Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile
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35 40 45

act agt gct tac tac tat tgg agc tgg atc cgc cag tca cca ggg aag 192
Thr Ser Ala Tyr Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys
50 55 60

gga ctg gag tgg att ggg agt atc tat tat agt ggg acc att ttc tcc 240
Gly Leu Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Thr Ile Phe Ser
65 70 75 80

aac cca tcc ctc aag agt cga gtc gcc atg tca gta ggc acg tcc aag 288
Asn Pro Ser Leu Lys Ser Arg Val Ala Met Ser Val Gly Thr Ser Lys
85 90 95

acc cag ttc tcc ctg agc ttg agt tct gtg acc gcc gcg gac acg gcc 336
Thr Gln Phe Ser Leu Ser Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

gtg tac tac tgt gcg aga ggt ctg ctc ctc acc att gga ctg acc aac 384
Val Tyr Tyr Cys Ala Arg Gly Leu Leu Leu Thr Ile Gly Leu Thr Asn
115 120 125

tac tac ttt gac tac tgg ggc ccg gga acc ctg gtc acc gtc ttc 429
Tyr Tyr Phe Asp Tyr Trp Gly Pro Gly Thr Leu Val Thr Val Phe
130 135 140

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<213> Pan troglodytes

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<222> (1)...(414)

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atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg      48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1               5                  10                  15

gtc ctg tcc cag gtg cag cta cag gag tcg ggc cca gga cta gtg aag      96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

ccg tca cag acc ctg tcc ctc acc tgc ggt gtc tct ggt gcc tcc atc     144
Pro Ser Gln Thr Leu Ser Leu Thr Cys Gly Val Ser Gly Ala Ser Ile
        35                  40                  45

aat agt ggt gtt cat tac tgg gcc tgg ata cgc cag cct gca gga aag     192
Asn Ser Gly Val His Tyr Trp Ala Trp Ile Arg Gln Pro Ala Gly Lys
    50                  55                  60

gga ctg gag tgg att ggc aat atc tat cat agt ggg agc gcc tac tac     240
Gly Leu Glu Trp Ile Gly Asn Ile Tyr His Ser Gly Ser Ala Tyr Tyr
65                  70                  75                  80

act cca tcc ctc gag agt cga gtc tcc atg tca ata gag acg tcc aag     288
Thr Pro Ser Leu Glu Ser Arg Val Ser Met Ser Ile Glu Thr Ser Lys
                85                  90                  95

agc cag ttc ttc cta aac tta aat tct ctg acc gcc gcg gac acg gct     336
Ser Gln Phe Phe Leu Asn Leu Asn Ser Leu Thr Ala Ala Asp Thr Ala
            100                 105                 110

atc tat tat tgt gcg aga cga cat act tcg tca gac tac ttt gac ttt     384
Ile Tyr Tyr Cys Ala Arg Arg His Thr Ser Ser Asp Tyr Phe Asp Phe
        115                 120                 125

tgg ggc cgc gga atc ctg gtc atc gtc tcc                             414
Trp Gly Arg Gly Ile Leu Val Ile Val Ser
    130                 135
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<213> Pan troglodytes

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<222> (1)...(427)

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Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Glu Gly
1 5 10 15

gtc cgt gca gac gtg cag ctg gtg cag tcc gga gca gag gtg aaa aag 96
Val Arg Ala Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

ccc ggg gag tct ctg aag atc tcc tgt aag gtc tct gga aat gaa ttt 144
Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Asn Glu Phe
35 40 45

acc aac tac tgg atc gcc tgg gtg cgc cag atg tcc ggg aaa ggc ctg 192
Thr Asn Tyr Trp Ile Ala Trp Val Arg Gln Met Ser Gly Lys Gly Leu
50 55 60

gag tgg atg ggg agc atc tat cct ggt gac tct gat acc aga tac aac 240
Glu Trp Met Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn
65 70 75 80

ccg tcc ttc caa ggc caa gtc acc ttt tca gcc gac aag tcc atc acc 288
Pro Ser Phe Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr
85 90 95

acc gcc tat ttg cag tgg agt agt ctg gag gcc tcg gac acc gcc atg 336
Thr Ala Tyr Leu Gln Trp Ser Ser Leu Glu Ala Ser Asp Thr Ala Met
100 105 110

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tac tac tgt gcg agc cga aat cac ttt gtt ttc ggg gaa gtt att act      384
Tyr Tyr Cys Ala Ser Arg Asn His Phe Val Phe Gly Glu Val Ile Thr
        115                 120                 125

act ttg acg gct ggg gcc agg gaa acc ctg ggt cac cgt ctc c            427
Thr Leu Thr Ala Gly Ala Arg Glu Thr Leu Gly His Arg Leu
    130                 135                 140


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      <213> Pan troglodytes

      <220>
      <221> CDS
      <222> (1)...(402)

      <400> 4
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Leu Gly Leu Arg Trp Val Phe Leu Val Ala Phe Leu Glu Gly Val Gln
 1               5                  10                  15

tgt gag gta cag ctg gtg gag tct ggg gga ggc ttg gta cag cct ggg       96
Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            20                  25                  30

ggg tcc ttg aca ctc tcc tgt gca gcc tct gga ttc acc ttc agt agg      144
Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg
        35                  40                  45

agt ggc atg cac tgg gtc cgc cag gct cca ggg aag gga ctg ggg tgg      192
Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gly Trp
     50                  55                  60

ctt gca tac att gat tat ggc agt att ttc ata tac tac tcg gac tca      240
Leu Ala Tyr Ile Asp Tyr Gly Ser Ile Phe Ile Tyr Tyr Ser Asp Ser
```

```
65                  70                  75                  80

gtg aag ggc cgc ttc acc atc tcc aga gac aac gcc aag aat tca ctc      288
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu
                85                  90                  95

tat ctg caa atg aac agc ctg aga gcc gac gac acg gct ttt tat tac      336
Tyr Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Phe Tyr Tyr
            100                 105                 110

tgt acg acc cat aat tgg ggg gag tta act gac tac tgg ggc cag gga      384
Cys Thr Thr His Asn Trp Gly Glu Leu Thr Asp Tyr Trp Gly Gln Gly
        115                 120                 125

acc ctg gtc acc gtc tcc                                              402
Thr Leu Val Thr Val Ser
    130


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      <213> Pan troglodytes

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      <221> CDS
      <222> (1)...(408)

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Met Glu Leu Gly Leu Arg Trp Val Phe Leu Val Ala Phe Leu Glu Gly
 1               5                  10                  15

gtc cag tgt gag gta cag ctg gtg gag tct ggg gga ggc ttg gta cag       96
Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30
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cct ggg ggg tcc ttg aca ctc tcc tgt gca gcc tct gga ttc acc ttc 144
Pro Gly Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

agt agg agt ggc atg cac tgg gtc cgc cag gct cca ggg aag gga ctg 192
Ser Arg Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

gag tgg ctt gca tac att gat tat ggc agt att ttc ata tac tac tcg 240
Glu Trp Leu Ala Tyr Ile Asp Tyr Gly Ser Ile Phe Ile Tyr Tyr Ser
65 70 75 80

gac tca gtg aag ggc cgc ttc acc atc tcc aga gac aac gcc aag aat 288
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

tca ctc tat ctg caa atg aac agc ctg aga gcc gac gac acg gct ttt 336
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Phe
100 105 110

tat tac tgt acg acc cat aat tgg ggg gag tta act gac tac tgg ggc 384
Tyr Tyr Cys Thr Thr His Asn Trp Gly Glu Leu Thr Asp Tyr Trp Gly
115 120 125

cag gga acc ctg gtc acc gtc tcc 408
Gln Gly Thr Leu Val Thr Val Ser
130 135

<210> 6
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<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(421)

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     <400> 6
atg atg ggg tca acc gcc atc ctc gcc ctc ctc ctg gct gtt ctc caa       48
Met Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln
 1               5                  10                  15

gga gtc tgt gca gag gtg cag ctg gtg cag tct gga gca gag gtg aaa       96
Gly Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
            20                  25                  30

aag ccc ggg gag tct ctg aag atc tcc tgt aag ggc tct gga tac agt      144
Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser
        35                  40                  45

ttt acc aac tac tgg atg ggc tgg gtg tgc cag atg ccc ggg aaa ggc      192
Phe Thr Asn Tyr Trp Met Gly Trp Val Cys Gln Met Pro Gly Lys Gly
    50                  55                  60

ccg gag tgc atg ggg atc atc tat cct gat gac tct gat acc aga tac      240
Pro Glu Cys Met Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr
65                  70                  75                  80

agc ccg tcc ttc caa ggc cag gtc acc atc tca gcc gac aag tcc atc      288
Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile
                85                  90                  95

agc acc gcc tac cta caa tgg agc aac ctg aag gcc tcg gac acc gcc      336
Ser Thr Ala Tyr Leu Gln Trp Ser Asn Leu Lys Ala Ser Asp Thr Ala
            100                 105                 110

ata tat tac tgt gcg aga tgt tat ggt tgg act act tgc gaa gct ttt      384
Ile Tyr Tyr Cys Ala Arg Cys Tyr Gly Trp Thr Thr Cys Glu Ala Phe
        115                 120                 125

gat atc tgg ggc caa ggg aca atg gtc acc gtc tct t                    421
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
    130                 135                 140
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<210> 7
<211> 417
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
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ttg tgg ttc ttc ctt ctc ctg gtg gca gct ccc aga tgg gtc ctg tcc 48
Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp Val Leu Ser
1 5 10 15

cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tca cag 96
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
20 25 30

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt ggt 144
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
35 40 45

agt tac tac tgg agt tgg atc cgg cag ccc gcc ggg aag cga ctg gag 192
Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu
50 55 60

tgg att ggg tat att tat tat agt ggg agt acc tac tac aac cca tcc 240
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
65 70 75 80

ctc aag agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc 288
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
85 90 95

tcc ctg aag ctg agc tct gtg acc gcc gca gac acg gcc gtc tat tac 336

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
100 105 110

tgt gcg aga tct ccc caa aac gta tta caa tct ttg gac tgc ttc gac 384
Cys Ala Arg Ser Pro Gln Asn Val Leu Gln Ser Leu Asp Cys Phe Asp
115 120 125

ccc tgg ggc cag gga acc ctg gtc acc gtc tcc 417
Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser
130 135

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<211> 369
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
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Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
1 5 10 15

cct ggg tcc tca gtg aag gtc tcc tgc aag gtt tcc gga ggc acc ttc 96
Pro Gly Ser Ser Val Lys Val Ser Cys Lys Val Ser Gly Gly Thr Phe
20 25 30

agc acc tat ggt ttc agc tgg gtg cgg cag gcc cct gga caa ggg ctt 144
Ser Thr Tyr Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
35 40 45

gag tgg atg gga atg atc atc cct atc gtt ggc aca gta aag tac gca 192
Glu Trp Met Gly Met Ile Ile Pro Ile Val Gly Thr Val Lys Tyr Ala
50 55 60

cag agg ttc cag ggc aga gtc tca att aat gcg gac aca tcc acg aat 240
Gln Arg Phe Gln Gly Arg Val Ser Ile Asn Ala Asp Thr Ser Thr Asn
65 70 75 80

ata gcc tac atg gag ctg acc agc ctg aga tct gag gac acg gcc gtc 288
Ile Ala Tyr Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val
85 90 95

tat tac tgt gcg aca gat ctg acg gtg act act aat gat gca ttt gat 336
Tyr Tyr Cys Ala Thr Asp Leu Thr Val Thr Thr Asn Asp Ala Phe Asp
100 105 110

atc tgg ggc caa ggg aca atg gtc acc gtc tct 369
Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
115 120

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<211> 423
<212> DNA
<213> Pan troglodytes

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<222> (1)...(423)

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atg gag ttt ggg ctg agc tgg ctt ttt ctt gtg gct att tta aaa ggt 48
Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

gtc cag tgt gag gtg cag ctg gtg gag tct ggg gaa ggc ttg gta aag 96
Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Glu Gly Leu Val Lys
20 25 30

cct ggg ggt tcc ctg aga ctc tcg tgt gca gcc tct gga ttc acc ttc 144

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Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

agt agt ttt ctt atg ttc tgg gtc cgc cag gct cca gaa aag ggg ctg      192
Ser Ser Phe Leu Met Phe Trp Val Arg Gln Ala Pro Glu Lys Gly Leu
    50                  55                  60

gag tgg gtc tca act att gat gtt agt ggt ggt aat atg tgg tac cga      240
Glu Trp Val Ser Thr Ile Asp Val Ser Gly Gly Asn Met Trp Tyr Arg
 65                  70                  75                  80

gac tct gtc aag ggc cga ttc acc atg tcc aga gac aat tcc aag aac      288
Asp Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn
                 85                  90                  95

aca ctg tat ctg caa atg acc agc ctg aga gcc gac gac acg gcc gtt      336
Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ala Asp Asp Thr Ala Val
            100                 105                 110

tac tat tgt gcg aga gag gga cga gac cct agc ggc act tgg gga tac      384
Tyr Tyr Cys Ala Arg Glu Gly Arg Asp Pro Ser Gly Thr Trp Gly Tyr
        115                 120                 125

ttt gac tac tgg ggc cag gga atc ctg gtc acc gtc tcc                  423
Phe Asp Tyr Trp Gly Gln Gly Ile Leu Val Thr Val Ser
    130                 135                 140
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<212> PRT
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<223> CDRII

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1               5                  10                  15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Thr Ser Ala
            20                  25                  30
Tyr Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu
        35                  40                  45
Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Thr Ile Phe Ser Asn Pro Ser
    50                  55                  60
Leu Lys Ser Arg Val Ala Met Ser Val Gly Thr Ser Lys Thr Gln Phe
65                  70                  75                  80
Ser Leu Ser Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95
Cys
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<210> 11
<211> 96
<212> PRT
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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
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1 5 10 15

Thr Leu Ser Leu Thr Cys Gly Val Ser Gly Ala Ser Ile Asn Ser Gly

20 25 30

Val His Tyr Trp Ala Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu

35 40 45

Trp Ile Gly Asn Ile Tyr His Ser Gly Ser Ala Tyr Tyr Thr Pro Ser

50 55 60

Leu Glu Ser Arg Val Ser Met Ser Ile Glu Thr Ser Lys Ser Gln Phe

65 70 75 80

Phe Leu Asn Leu Asn Ser Leu Thr Ala Asp Thr Ala Ile Tyr Tyr Cys

85 90 95

<210> 12

<211> 96

<212> PRT

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<221> DOMAIN

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<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 12

Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Asn Glu Phe Thr Asn Tyr

20 25 30

Trp Ile Ala Trp Val Arg Gln Met Ser Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Glu Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

<210> 13
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<400> 13
Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Asn Glu Phe Thr Asn Tyr
20 25 30
Trp Ile Ala Trp Val Arg Gln Met Ser Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Glu Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

<210> 14
<211> 96
<212> PRT
<213> Pan troglodytes

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<221> DOMAIN
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<400> 14

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 1               5                  10                  15
Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Ser
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gly Trp Leu
        35                  40                  45
Ala Tyr Ile Asp Tyr Gly Ser Ile Phe Ile Tyr Tyr Ser Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Phe Tyr Tyr Cys
                85                  90                  95
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<210> 15
<211> 96
<212> PRT
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<220>
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<223> CDRI

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<223> CDRII

<400> 15

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

Trp Met Gly Trp Val Cys Gln Met Pro Gly Lys Gly Pro Glu Cys Met
35 40 45

Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Asn Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

<210> 16
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<400> 16

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe

65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr

85 90 95

Cys

<210> 17

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<212> PRT

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<222> (50)...(66)

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<400> 17

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15

Ser Val Lys Val Ser Cys Lys Val Ser Gly Gly Thr Phe Ser Thr Tyr

20 25 30

Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Met Ile Ile Pro Ile Val Gly Thr Val Lys Tyr Ala Gln Arg Phe

50 55 60

Gln Gly Arg Val Ser Ile Asn Ala Asp Thr Ser Thr Asn Ile Ala Tyr

65 70 75 80

Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

<210> 18

<211> 96

<212> PRT

<213> Pan troglodytes

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Glu Val Gln Leu Val Glu Ser Gly Glu Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30
Leu Met Phe Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45
Ser Thr Ile Asp Val Ser Gly Gly Asn Met Trp Tyr Arg Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Thr Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

<210> 19
<211> 381
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(381)

<400> 19
atg agg gtc cct gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc tca 48
Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Ser

```
 1               5                   10                  15

ggt gcc aga tgt gac atc cag atg acc cag ttt cca tcc tcc ctg tct       96
Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Ser
            20                  25                  30

gca tct gta gga gac aga gtc acc atc act tgc cag tca agt cag agc      144
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser
        35                  40                  45

att tac aac tgc ttg agt tgg tat cag cag aaa cca ggg aag gcc cct      192
Ile Tyr Asn Cys Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
    50                  55                  60

aca ctc cta atc tat ggt gca ttc acc ttg aat agt ggg gtc cca tca      240
Thr Leu Leu Ile Tyr Gly Ala Phe Thr Leu Asn Ser Gly Val Pro Ser
65                  70                  75                  80

aga ttc agt ggc agt gga tct ggc aca gat ttc act ctc acc atc agc      288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

aat ctg caa cct gaa gat ttt gca aca tat tac tgt cag cgt ggt tac      336
Asn Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Arg Gly Tyr
            100                 105                 110

ggc aca cag ctc act ttc ggt gga ggg acc aag gtg gag atc aag          381
Gly Thr Gln Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125
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<210> 20
<211> 384
<212> DNA
<213> Pan troglodytes

<220>
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<221> CDS
<222> (1)...(384)

<400> 20

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atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg        48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1               5                  10                  15

ctc cca ggt acc aga tgt gac atc cag atg acc cag tct cca tcc tcc        96
Leu Pro Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

ctg tct gca tct gta gga gac aga gtc acc atc act tgc cgg gcc agt       144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

cag ggc att agc aat tat tta gcc tgg tat cag cag aaa cca ggg aaa       192
Gln Gly Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

gcc cct aag ctc ctc atc tat tat gca tcc aga ttg gaa agt ggg gtc       240
Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Arg Leu Glu Ser Gly Val
 65                  70                  75                  80

cca tca agg ttc agc ggc agt gga tct ggg acg gat tac act ctc acc       288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
                 85                  90                  95

atc agc agc ctg cag cct gaa gat ttt gca act tat tac tgt caa cag       336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

tat aac agt aac ccc ttt tcg gtg gag gga cca agg tgg aga tca aac       384
Tyr Asn Ser Asn Pro Phe Ser Val Glu Gly Pro Arg Trp Arg Ser Asn
        115                 120                 125
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<210> 21

<211> 384

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(384)

<400> 21

atg tcg cca tca caa ctc att ggg ttt ctg ctg ctc tgg gtt cca gcc 48
Met Ser Pro Ser Gln Leu Ile Gly Phe Leu Leu Leu Trp Val Pro Ala
1 5 10 15

tcc agg ggt gaa att gtg ctg act cag tct cca gac ttt cag tct gtg 96
Ser Arg Gly Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val
20 25 30

cct cca aag gag aaa gtc acc atc acc tgc cgg gcc agt cag agc att 144
Pro Pro Lys Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile
35 40 45

ggt agt agc tta cac tgg tac cag cag aaa cca ggt cag tct cca aag 192
Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
50 55 60

ctc ctc atc aag tat gct tcc cag tcc atc tca ggg gtc ccc tcg agg 240
Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg
65 70 75 80

ttc agt ggc agt gga tct ggg aca gat ttc acc ctc acc atc aat agc 288
Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser
85 90 95

ctg gaa gct gaa gat gct gca acg tat tac tgt cag caa agt agt aat 336
Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Asn
100 105 110

tta cct cat acg ctc act ttc ggt gga ggg acc aag gtg gag atc aaa 384
Leu Pro His Thr Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

<210> 22
<211> 372
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(372)

<400> 22
gtc cct gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc tca ggt gcc 48
Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Ser Gly Ala
1 5 10 15

aga tgt gac atc cag atg acc cag tct cca tcc tcc ctg tct gca tct 96
Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
20 25 30

gta gga gac aga gtc acc atc act tgc cag gca agt cag agc att agc 144
Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser
35 40 45

aac tat ttg agt tgg tat cag cag aaa cca ggg aaa gcc cct aag ctc 192
Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
50 55 60

ctg atc tat gat gca tcc act ttg caa agt ggg gtc cca tca agg ttc 240
Leu Ile Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe
65 70 75 80

agt ggc agt gga tct ggg aca gat ttc act ctc acc atc agc agt ctg 288

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
85 90 95

caa cct gaa gat ttt gca aca tat tac tgt cag cgt ggt tac ggt aca 336
Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Arg Gly Tyr Gly Thr
100 105 110

ctc act ttc ggt gga ggg acc aag gtg gag atc aaa 372
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120

<210> 23
<211> 384
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(384)

<400> 23
atg gaa gcc cca gcg cag ctt ctc ttc ctc ctg cta ctc tgg ctc cca 48
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

gat acc acc gga gaa ata gtg ttg acg cag tct cca gcc acc ctg tct 96
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30

ttg tct cca ggg gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt 144
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

gtt agc agg tac tta gcc tgg tac cag cag aaa cct ggc cag gct ccc 192
Val Ser Arg Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60

agg ctc ctc atc tat ggt gca tcc aac agg gcc act ggc atc cca gcc 240
Arg Leu Leu Ile Tyr Gly Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65 70 75 80

agg ttc agt ggc agt ggg tct agg aca gac ttc act ctc acc atc agc 288
Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95

agc gtg gag cct gaa gat ttt gca gtt tat tac tgt cag cag tat aat 336
Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn
100 105 110

aac cag cct ctg atc gcc ttc ggc caa ggg aca cga ctg gag att aaa 384
Asn Gln Pro Leu Ile Ala Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
115 120 125

<210> 24
<211> 387
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(387)

<400> 24
atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

ttc cca ggt gcc aaa tgt gac atc cag atg acc cag tct cct tcc acc 96
Phe Pro Gly Ala Lys Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
20 25 30

ctg tct gcc tcc ata gga gac aga gtc acc atc act tgt cgg gct agt 144

Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

cag ggc atc tat aat tat ttg aat tgg tat cag caa aaa cca ggg aga 192
Gln Gly Ile Tyr Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg
50 55 60

gcc cct gga ctc ctc atc ttt ggt gcc agg aat ttg gag act ggg gtc 240
Ala Pro Gly Leu Leu Ile Phe Gly Ala Arg Asn Leu Glu Thr Gly Val
65 70 75 80

cca tca aca ttc agc ggc agt ggt tcc ggg aca cac ttc act ctc acc 288
Pro Ser Thr Phe Ser Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr
85 90 95

atc agc agc ctg cag cct ggt gat ttt gcg act tat tac tgt cag caa 336
Ile Ser Ser Leu Gln Pro Gly Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

tat tat act acc ccg tat act ttt ggc cag ggg acc aag ctg gag atc 384
Tyr Tyr Thr Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

aaa 387

<210> 25
<211> 387
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(387)

<400> 25
atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctc tgt 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys

1 5 10 15

ttc cca ggt gcc aga tgt gac atc cag atg acc cag tct cca tcc tca 96
Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

ctg tct gct tct gta gga gac aga gtc acc atc tct tgt cgg gcg agt 144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
35 40 45

ctg gat att agc acc tgg tta gcc tgg tat cag cag aaa cca ggg aaa 192
Leu Asp Ile Ser Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

gcc cct aag ccc ctg atc tat gct gca tcc act ttg cca agt ggg gtc 240
Ala Pro Lys Pro Leu Ile Tyr Ala Ala Ser Thr Leu Pro Ser Gly Val
65 70 75 80

cca tcg agg ttc agc ggc agt gga tct ggg aca gat ttc act ctc acc 288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

atc agc agc ctg cag cct gaa gat tct gca act tat tac tgc cga caa 336
Ile Ser Ser Leu Gln Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Arg Gln
100 105 110

tat aat agt tat ccg ctc act ttc ggt gga ggg acc aag gtg gag atc 384
Tyr Asn Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

aag 387

<210> 26
<211> 372
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(372)

<400> 26

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tct act cag ctc ctg ggg ctc ctg ctg ctc tgg ctc cca ggt gcc aaa        48
Ser Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Pro Gly Ala Lys
 1               5                  10                  15

tgt gac atc cag atg acc cag tct cct tcc acc ctg tct gca tct gta        96
Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val
            20                  25                  30

gga gac aga gtc acc atc act tgc cgg gcc agt cag ggt att agt agc       144
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser
        35                  40                  45

tgg tta gcc tgg tat cag cag aaa cca ggg aaa gcc cct aag ctc ctg       192
Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
    50                  55                  60

atc tat aag gca tct agt tta gaa agt ggg gtc cca tca agg ttc agc       240
Ile Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser
 65                  70                  75                  80

ggc agt gga tct ggg aca gaa ttc act ctc acc atc agc agc ctg cag       288
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
                85                  90                  95

cct gat gat ttt gca act tat tac tgc caa cag tat agt agt tac cct       336
Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro
            100                 105                 110

cga acg ttc ggc caa ggg acc aag ctg gaa atc aaa                       372
Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120
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<210> 27
<211> 387
<212> DNA
<213> Pan troglodytes

<220>
<221> CDS
<222> (1)...(387)

<400> 27
atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

ctc tca ggt acc aga tgt gac atc cag atg acc cag tct cca tcc tcc 96
Leu Ser Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

ctg tct gca tct gta gga gac aga gtc acc atc act tgc cgg gca agt 144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

cag agc att agc aac tat ttg agt tgg tat cag cag aaa cca ggg aaa 192
Gln Ser Ile Ser Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

gcc cct aag ctc ctg atc tat tat gca tcc act ttg caa agt ggg gtc 240
Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Gln Ser Gly Val
65 70 75 80

cca tca agg ttc agt ggc agt gga tct ggg aca gat ttc act ctc acc 288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

atc agc agt ctg caa cct gaa gat ttt gca act tat tac tgt cag cat 336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His

100 105 110

ggt tac ggt aca cat ccc act ttc ggt gga ggg acc aag gtg gag atc 384
Gly Tyr Gly Thr His Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

aaa 387

<210> 28
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 28
Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser Ile Tyr Asn Cys
20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Thr Leu Leu Ile
35 40 45
Tyr Gly Ala Phe Thr Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys
85

<210> 29

<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 29

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Tyr Ala Ser Arg Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys
                85
```

<210> 30
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 30

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Pro Pro Lys
1 5 10 15
Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45
Lys Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65 70 75 80
Glu Asp Ala Ala Thr Tyr Tyr Cys
85

<210> 31
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 31

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Asn Tyr
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys
85

<210> 32
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 32
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Arg Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys
85

<210> 33

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Tyr Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Gly Leu Leu Ile
35 40 45

Phe Gly Ala Arg Asn Leu Glu Thr Gly Val Pro Ser Thr Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Gly Asp Phe Ala Thr Tyr Tyr Cys
85

<210> 34

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 34

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Leu Asp Ile Ser Thr Trp
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Pro Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Thr Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Ser Ala Thr Tyr Tyr Cys
                85
```

<210> 35
<211> 88
<212> PRT
<213> Pan troglodytes

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 35

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
```

```
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Asp Asp Phe Ala Thr Tyr Tyr Cys
                85


      <210> 36
      <211> 88
      <212> PRT
      <213> Pan troglodytes

      <220>
      <221> DOMAIN
      <222> (24)...(34)
      <223> CDRI

      <221> DOMAIN
      <222> (50)...(66)
      <223> CDRII

      <400> 36
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
            20                  25                  30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Tyr Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys
                85
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<210> 37

<211> 408

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(408)

<400> 37

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atg gag ttt gga ctg agc tgg gtt ttc ctt gtc gct att ttc aaa ggt       48
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Phe Lys Gly
 1               5                  10                  15

gtc cag tgt gaa gtg cag ttg gtg gag tct ggg gga ggc ttg gta cag       96
Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

ccg ggg ggg tcc ctg aga ctc gcc tgt gta ggc tct gga ttc gcc ttc      144
Pro Gly Gly Ser Leu Arg Leu Ala Cys Val Gly Ser Gly Phe Ala Phe
        35                  40                  45

aga aac acc agg atg cac tgg att cga cag act cca gga aag agg ctg      192
Arg Asn Thr Arg Met His Trp Ile Arg Gln Thr Pro Gly Lys Arg Leu
    50                  55                  60

gag tgg gtg gcc gac ata aag ttt gat gga agt gat ttt tac tat gta      240
Glu Trp Val Ala Asp Ile Lys Phe Asp Gly Ser Asp Phe Tyr Tyr Val
65                  70                  75                  80

gac tct gtg aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac      288
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

tcc ctc tat ctg gaa atg aac agc ctg aga cct gat gac aca gcc gtc      336
Ser Leu Tyr Leu Glu Met Asn Ser Leu Arg Pro Asp Asp Thr Ala Val
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100 105 110

tat ttc tgt gtg aga gaa tac aga gat gga ctg gat gtc tgg ggc cgg 384
Tyr Phe Cys Val Arg Glu Tyr Arg Asp Gly Leu Asp Val Trp Gly Arg
115 120 125

gga gtt ctg gtc acc gtc tcc tca 408
Gly Val Leu Val Thr Val Ser Ser
130 135

<210> 38
<211> 381
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(381)

<400> 38
gtg aca gct ccc aga tgg gtc ctg tcc cag gtg caa ttg cag gag tcg 48
Val Thr Ala Pro Arg Trp Val Leu Ser Gln Val Gln Leu Gln Glu Ser
1 5 10 15

ggc cca gga ctg gtg aag cct tcg gag acc ctg tcc ctc act tgt act 96
Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr
20 25 30

gtc tct ggt gac tcc atc acc act gtc ttc tgg agc tgg ctc cgc cag 144
Val Ser Gly Asp Ser Ile Thr Thr Val Phe Trp Ser Trp Leu Arg Gln
35 40 45

tcg cca ggg att ggg ctg gag tgg att ggg aat ttt gct ggt agt act 192
Ser Pro Gly Ile Gly Leu Glu Trp Ile Gly Asn Phe Ala Gly Ser Thr
50 55 60

ccg gaa acg aac tac aat ccc tcc ctc aag aat cga gcc acc att tca 240
Pro Glu Thr Asn Tyr Asn Pro Ser Leu Lys Asn Arg Ala Thr Ile Ser
65 70 75 80

aaa gac acg ccc acg aat caa ttt ttc ctg agg ctg acg tct gtg acc 288
Lys Asp Thr Pro Thr Asn Gln Phe Phe Leu Arg Leu Thr Ser Val Thr
85 90 95

gcc gcg gac acg gcc gtc tac ttc tgt gcg aga gga ggg gga gcc ggc 336
Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Gly Ala Gly
100 105 110

aac cca ctc act tgg ggc cag gga gtc cag gtc acc gtc tcc tca 381
Asn Pro Leu Thr Trp Gly Gln Gly Val Gln Val Thr Val Ser Ser
115 120 125

<210> 39
<211> 417
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(417)

<400> 39
atg ggg tca act gcc atc ctc gcc ctc ctc ctg gct gtt ctc caa gga 48
Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
1 5 10 15

gtc tgt gcc gag gtg cat ctg gtg cag tct gga gca cag gtg aaa agg 96
Val Cys Ala Glu Val His Leu Val Gln Ser Gly Ala Gln Val Lys Arg
20 25 30

ccc ggg gaa tct ctg agg atc tcc tgt aag act tct gga tac acc ttt 144
Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe

35 40 45

acc gac agc tgg atc agc tgg gtg cgc cag atg ccc ggg aaa ggc ctg 192
Thr Asp Ser Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu
50 55 60

gag tgg atg gga aac atc tat cct ggt gat tct gat tcc aga tac aac 240
Glu Trp Met Gly Asn Ile Tyr Pro Gly Asp Ser Asp Ser Arg Tyr Asn
65 70 75 80

ccg tcc ttc caa ggc cgc gtc act atc tca gtc gac aag tcc atc agt 288
Pro Ser Phe Gln Gly Arg Val Thr Ile Ser Val Asp Lys Ser Ile Ser
85 90 95

acc acc tac ctg cag tgg agc agc ctg aag gcc tcg gac act gcc aca 336
Thr Thr Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Thr
100 105 110

tat tac tgt gcg aag ata gat agc aac tac tac agc cgg ttc gaa gtc 384
Tyr Tyr Cys Ala Lys Ile Asp Ser Asn Tyr Tyr Ser Arg Phe Glu Val
115 120 125

tgg ggc ccc gga gtc atg gtc acc gtc tcc tca 417
Trp Gly Pro Gly Val Met Val Thr Val Ser Ser
130 135

<210> 40
<211> 423
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(423)

<400> 40

atg	aag	cac	ctg	tgg	ttc	ttc	ctc	ctc	ctg	gtg	gca	gct	cct	aga	tgg	48
Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp	
1				5					10					15		
gtc	ctg	tcc	cag	gtg	cag	ttg	cag	gag	tcg	ggc	cca	gga	gtg	gtg	aag	96
Val	Leu	Ser	Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Val	Val	Lys	
			20					25					30			
cct	tcg	gag	acc	ctg	tcc	ctc	acc	tgc	act	gtc	tct	ggt	ggc	tcc	ttc	144
Pro	Ser	Glu	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Phe	
		35					40					45				
agt	act	tac	tac	tgg	aat	tgg	atc	cgc	cag	ccc	cca	ggg	aag	gga	ctg	192
Ser	Thr	Tyr	Tyr	Trp	Asn	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	
	50					55					60					
gag	tgg	att	gga	tat	atc	ggt	ggt	ggt	ggt	ggt	cgc	ccc	aac	tac	aat	240
Glu	Trp	Ile	Gly	Tyr	Ile	Gly	Gly	Gly	Gly	Gly	Arg	Pro	Asn	Tyr	Asn	
65					70					75					80	
tcc	tcc	ctc	aag	agt	cgc	atc	acc	ctg	tca	cta	gac	gcg	tcc	aag	aac	288
Ser	Ser	Leu	Lys	Ser	Arg	Ile	Thr	Leu	Ser	Leu	Asp	Ala	Ser	Lys	Asn	
				85					90					95		
cag	ttc	tcc	ctg	aac	ctg	agc	tct	gtg	acc	gcc	gcg	gac	acg	gcc	gtg	336
Gln	Phe	Ser	Leu	Asn	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	
			100					105					110			
tac	tac	tgt	gcc	aga	gat	cgg	ggc	tac	ggt	gcc	agc	aat	gat	gct	ttt	384
Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Gly	Tyr	Gly	Ala	Ser	Asn	Asp	Ala	Phe	
		115					120					125				
gat	ttc	tgg	ggc	caa	ggg	ctc	agg	gtc	acc	gtc	tct	tca				423
Asp	Phe	Trp	Gly	Gln	Gly	Leu	Arg	Val	Thr	Val	Ser	Ser				
	130					135					140					

<210> 41
<211> 411
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(411)

<400> 41
atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca act cct aaa tgg 48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Thr Pro Lys Trp
1 5 10 15

gtc ctg tcc cag gtg cag ttg cat gag tcg ggc cct gga ctg ctg aag 96
Val Leu Ser Gln Val Gln Leu His Glu Ser Gly Pro Gly Leu Leu Lys
20 25 30

cct tcg gag acc ctg tcc ctc acc tgc aat gtc tcc ggt gac tcc ccc 144
Pro Ser Glu Thr Leu Ser Leu Thr Cys Asn Val Ser Gly Asp Ser Pro
35 40 45

act aag tcc acg tgg aac tgg gtc cgc cag tcc cca ggg aag cca ctg 192
Thr Lys Ser Thr Trp Asn Trp Val Arg Gln Ser Pro Gly Lys Pro Leu
50 55 60

gaa tgg att ggt cat gtc ggt tct ggt gga ggt ggc ccc gtt tac aac 240
Glu Trp Ile Gly His Val Gly Ser Gly Gly Gly Gly Pro Val Tyr Asn
65 70 75 80

gtc ttc ttg acg ggt cgc gtc tcc atg tct cta gac gct tca aag aag 288
Val Phe Leu Thr Gly Arg Val Ser Met Ser Leu Asp Ala Ser Lys Lys
85 90 95

ctt ctc tcc ctg gcc tta gca tct gtg acc gcc gcc gac tcg gcc gtc 336
Leu Leu Ser Leu Ala Leu Ala Ser Val Thr Ala Ala Asp Ser Ala Val
100 105 110

tat tac tgt gtc aga tcg acg gca tta ttt tcg ttg gat gtc tgg ggc 384
Tyr Tyr Cys Val Arg Ser Thr Ala Leu Phe Ser Leu Asp Val Trp Gly
115 120 125

cgg gga ctt ctg gtc acc gtc tcc tca 411
Arg Gly Leu Leu Val Thr Val Ser Ser
130 135

<210> 42
<211> 442
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(441)

<400> 42
atg gag ttg gga ctg agc tgg gtt ttc ctt ctt gtt gct att tta aaa 48
Met Glu Leu Gly Leu Ser Trp Val Phe Leu Leu Val Ala Ile Leu Lys
1 5 10 15

ggt gtc cag tgt gac aag cag ctg gtg cag tcg ggg gga ggc ttg gtc 96
Gly Val Gln Cys Asp Lys Gln Leu Val Gln Ser Gly Gly Gly Leu Val
20 25 30

cag cct ggc ggg tct ctg aga ctc gcc tgt gta gcc tcc gga ttc ccc 144
Gln Pro Gly Gly Ser Leu Arg Leu Ala Cys Val Ala Ser Gly Phe Pro
35 40 45

ttc agt gac tat tac atg agt tgg gtc cgc cag gct cca ggg aag ggg 192
Phe Ser Asp Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
50 55 60

ttg gag tgg ctt gga tta att aaa acc aat cct gat ggt gga acg aca 240

Leu Glu Trp Leu Gly Leu Ile Lys Thr Asn Pro Asp Gly Gly Thr Thr
65 70 75 80

gat tac gcc gcg tct gtg aaa ggc aga ttt atc atc tca cga gat gat 288
Asp Tyr Ala Ala Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp
85 90 95

tca aag aac tca ctg ttc ctt caa atg aac agc ctg aaa acc gag gac 336
Ser Lys Asn Ser Leu Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp
100 105 110

acg gcc gtg tat tac tgc acc aca gaa gtg ttg gtg gtg tct gct att 384
Thr Ala Val Tyr Tyr Cys Thr Thr Glu Val Leu Val Val Ser Ala Ile
115 120 125

caa ctc att gga tgt ctg ggg ccc ggg gag ttg tgg tca ccc gtc tct 432
Gln Leu Ile Gly Cys Leu Gly Pro Gly Glu Leu Trp Ser Pro Val Ser
130 135 140

ttc cgc ttc a 442
Phe Arg Phe
145

<210> 43
<211> 407
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(405)

<400> 43
atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca gct ccc aga tgg 48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

gtc ctg tcc cag gtg cag ttg gag gag tcg ggc cca gga ctg gtg aag 96
Val Leu Ser Gln Val Gln Leu Glu Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

ccc tcg gag acc ctg tcc ctc acc tgc gct gtg tct ggt ggc ctc att 144
Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Leu Ile
35 40 45

act gga aac tac tgg aac tgg ctc cgg cag tca gaa ggg aag gga ctg 192
Thr Gly Asn Tyr Trp Asn Trp Leu Arg Gln Ser Glu Gly Lys Gly Leu
50 55 60

gag tgg att ggc cat att ggt ggt agt agt ggg aac acc ggc tac aac 240
Glu Trp Ile Gly His Ile Gly Gly Ser Ser Gly Asn Thr Gly Tyr Asn
65 70 75 80

tcc gct ttc gag agt cgc gtc acc ttg tca aga gac acg gcc aag aat 288
Ser Ala Phe Glu Ser Arg Val Thr Leu Ser Arg Asp Thr Ala Lys Asn
85 90 95

cgg ttc tcc ctg aaa ctg acc tct gtg acc gcc gca gat tcg gcc gtc 336
Arg Phe Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Ser Ala Val
100 105 110

tat tac tgt gcg aga tcg ggt ttt acc ggc acc gac ttc ttt tac tat 384
Tyr Tyr Cys Ala Arg Ser Gly Phe Thr Gly Thr Asp Phe Phe Tyr Tyr
115 120 125

tgg ggc ccg ggg aag tct tgg tc 407
Trp Gly Pro Gly Lys Ser Trp
130 135

<210> 44
<211> 420
<212> DNA

<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(420)

<400> 44

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atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca gct ccc aga tgg      48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1               5                  10                  15

gtc ctg tcc cag gtt caa cta cag gag tcg ggc cca gga ctg atg aag      96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Met Lys
             20                  25                  30

cct tcg gag acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc     144
Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile
         35                  40                  45

agc ggt ggt ttt ggc tgg ggc tgg atc cgt cag tcc ccg ggg aag ggg     192
Ser Gly Gly Phe Gly Trp Gly Trp Ile Arg Gln Ser Pro Gly Lys Gly
     50                  55                  60

ctg gaa tgg att gga agt ttc tat act act act gga aat acc ttc tcc     240
Leu Glu Trp Ile Gly Ser Phe Tyr Thr Thr Thr Gly Asn Thr Phe Ser
 65                  70                  75                  80

aac ccc tcc ctc aag agt cga gtc acc att tca gcg gac acg tcc aag     288
Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Ala Asp Thr Ser Lys
                 85                  90                  95

aac cag ttc tcc ctg aga ctg acc tct gtg acc gcc gcg gac acg gcc     336
Asn Gln Phe Ser Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

gtt tat tac tgt gcg aga gat ctc tat agc agc ggc tat aaa ttt tac     384
Val Tyr Tyr Cys Ala Arg Asp Leu Tyr Ser Ser Gly Tyr Lys Phe Tyr
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        115                 120                 125

tac tgg ggc cag gga gtc ctg gtc acc gtc tcc tca                    420
Tyr Trp Gly Gln Gly Val Leu Val Thr Val Ser Ser
    130                 135                 140


      <210> 45
      <211> 98
      <212> PRT
      <213> Macaca cynomolgus

      <220>
      <221> DOMAIN
      <222> (31)...(35)
      <223> CDRI

      <221> DOMAIN
      <222> (50)...(66)
      <223> CDRII

      <400> 45
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ala Cys Val Gly Ser Gly Phe Ala Phe Arg Asn Thr
            20                  25                  30
Arg Met His Trp Ile Arg Gln Thr Pro Gly Lys Arg Leu Glu Trp Val
        35                  40                  45
Ala Asp Ile Lys Phe Asp Gly Ser Asp Phe Tyr Tyr Val Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Glu Met Asn Ser Leu Arg Pro Asp Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95
Val Arg
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<210> 46

<211> 98

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 46

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Thr Thr Val
20 25 30

Phe Trp Ser Trp Leu Arg Gln Ser Pro Gly Ile Gly Leu Glu Trp Ile
35 40 45

Gly Asn Phe Ala Gly Ser Thr Pro Glu Thr Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Asn Arg Ala Thr Ile Ser Lys Asp Thr Pro Thr Asn Gln Phe Phe
65 70 75 80

Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg

<210> 47

<211> 98

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(35)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 47

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Glu Val His Leu Val Gln Ser Gly Ala Gln Val Lys Arg Pro Gly Glu
 1               5                  10                  15
Ser Leu Arg Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Asp Ser
            20                  25                  30
Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Asn Ile Tyr Pro Gly Asp Ser Asp Ser Arg Tyr Asn Pro Ser Phe
    50                  55                  60
Gln Gly Arg Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Thr Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95
Ala Lys
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<210> 48
<211> 98
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (31)...(35)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 48

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Val Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe Ser Thr Tyr
20 25 30

Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Gly Gly Gly Gly Gly Arg Pro Asn Tyr Asn Ser Ser Leu
50 55 60

Lys Ser Arg Ile Thr Leu Ser Leu Asp Ala Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Asn Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg

<210> 49

<211> 98

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 49

Gln Val Gln Leu His Glu Ser Gly Pro Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Asn Val Ser Gly Asp Ser Pro Thr Lys Ser
20 25 30

Thr Trp Asn Trp Val Arg Gln Ser Pro Gly Lys Pro Leu Glu Trp Ile
35 40 45

Gly His Val Gly Ser Gly Gly Gly Gly Pro Val Tyr Asn Val Phe Leu
    50   55   60
Thr Gly Arg Val Ser Met Ser Leu Asp Ala Ser Lys Lys Leu Leu Ser
65   70   75   80
Leu Ala Leu Ala Ser Val Thr Ala Ala Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Val Arg

<210> 50
<211> 100
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (31)...(35)
<223> CDRI

<221> DOMAIN
<222> (50)...(68)
<223> CDRII

<400> 50
Asp Lys Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ala Cys Val Ala Ser Gly Phe Pro Phe Ser Asp Tyr
            20   25   30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
        35   40   45
Gly Leu Ile Lys Thr Asn Pro Asp Gly Gly Thr Thr Asp Tyr Ala Ala
    50   55   60
Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asn Ser
65   70   75   80
Leu Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85   90   95
Tyr Cys Thr Thr

100

<210> 51
<211> 98
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (31)...(35)
<223> CDRI

<221> DOMAIN
<222> (50)...(66)
<223> CDRII

<400> 51
Gln Val Gln Leu Glu Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Leu Ile Thr Gly Asn
            20   25   30
Tyr Trp Asn Trp Leu Arg Gln Ser Glu Gly Lys Gly Leu Glu Trp Ile
        35   40   45
Gly His Ile Gly Gly Ser Ser Gly Asn Thr Gly Tyr Asn Ser Ala Phe
    50   55   60
Glu Ser Arg Val Thr Leu Ser Arg Asp Thr Ala Lys Asn Arg Phe Ser
65   70   75   80
Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg

<210> 52
<211> 99
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (31)...(36)
<223> CDRI

<221> DOMAIN
<222> (51)...(67)
<223> CDRII

<400> 52
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Met Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Gly Gly
20 25 30
Phe Gly Trp Gly Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
35 40 45
Ile Gly Ser Phe Tyr Thr Thr Thr Gly Asn Thr Phe Ser Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Ala Asp Thr Ser Lys Asn Gln Phe
65 70 75 80
Ser Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95
Cys Ala Arg

<210> 53
<211> 390
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(390)

<400> 53
atg gac ata agg gtc ccc gtg cag ctc ctg ggg ctc ctg ttg ctc tgg 48
Met Asp Ile Arg Val Pro Val Gln Leu Leu Gly Leu Leu Leu Leu Trp

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 1               5                   10                  15

ctc cga ggt gcc aga tgt gac atc cag atg acc cag tct cca tcc tcc       96
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
                20                  25                  30

ctg tct aca tct gta gga gac act gtc acc atc act tgc cgg gcg agt      144
Leu Ser Thr Ser Val Gly Asp Thr Val Thr Ile Thr Cys Arg Ala Ser
            35                  40                  45

caa ggc att gac acg gag tta gcc tgg tat cag cag aaa cca ggt aaa      192
Gln Gly Ile Asp Thr Glu Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
        50                  55                  60

gcc ccc aca ctc ctg atc tct gat gcc tcc agg ttg cag acg ggg gtc      240
Ala Pro Thr Leu Leu Ile Ser Asp Ala Ser Arg Leu Gln Thr Gly Val
 65                  70                  75                  80

tca tct cgg ttc agc ggc agt gga tct gga aca gat ttc act ctc acc      288
Ser Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                 85                  90                  95

atc aac agc ctg cag cct gaa gat att gcg act tat tac tgt caa cag      336
Ile Asn Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln
                100                 105                 110

gat aat agt ttt cca ctc act ttc ggc gga ggg acc aag gtg gag atc      384
Asp Asn Ser Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
            115                 120                 125

aaa cga                                                              390
Lys Arg
    130
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<210> 54

<211> 384

<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(384)

<400> 54

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gtc ttc att tcc ctg ttg ctc tgg atc tct ggt gcc tgt ggg gac att       48
Val Phe Ile Ser Leu Leu Leu Trp Ile Ser Gly Ala Cys Gly Asp Ile
 1               5                  10                  15

gtg atg acc cag tct cca gac tcc ctg gct gtg tct ctg gga gag agg       96
Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg
            20                  25                  30

gtc acc atc aat tgt aag tcc agc cag agt ctt tta tac agc tcc aac      144
Val Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Ser Asn
        35                  40                  45

aat aag aac tac tta gcc tgg tac cag caa aaa cca gga cag gct cct      192
Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60

caa cta ctc att tac tgg gca tct acc cgg gaa tcc ggg gtc cct aat      240
Gln Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asn
65                  70                  75                  80

cga ttt agt ggc agc ggc tct ggg aca gat ttc act ctc acc atc agt      288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

ggc ctg cag gct gaa gat gtg gca gtg tat tac tgt caa cag tat tat      336
Gly Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr
            100                 105                 110

gat atg ccc gac agt ttt ggc cag ggg acc aaa gtg gac atc aaa cga      384
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Asp Met Pro Asp Ser Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg
115 120 125

<210> 55
<211> 399
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(399)

<400> 55
atg agg ctc cct gct cag ctc ctg ggg ctg cta ttg ctc tgc gtc ccc 48
Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys Val Pro
1 5 10 15

gga tcc agt ggg gat gtt gtg atg act cag tct cca ctc tcc ctg ccc 96
Gly Ser Ser Gly Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro
20 25 30

gtc atc cct gga cag cca gcc tcc atc tcc tgc agg tct agt caa agc 144
Val Ile Pro Gly Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
35 40 45

ctt gta cat agt gac ggg aaa acc tac ttg aat tgg tta caa cag aag 192
Leu Val His Ser Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys
50 55 60

cca ggc caa cct cca aga ctc ctg att tat cag gtt tct aac cgg cac 240
Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Gln Val Ser Asn Arg His
65 70 75 80

tct ggg gtc cca gac aga ttc agc ggc agt ggg gca ggg aca gac ttc 288
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe
85 90 95

aca ctg aaa atc agc aga gtg gag act gag gat gtt ggg gtt tat tcc 336
Thr Leu Lys Ile Ser Arg Val Glu Thr Glu Asp Val Gly Val Tyr Ser
100 105 110

tgc gtg caa ggt aca cac tgg ccg tgg acg ttc ggc caa ggg acc aag 384
Cys Val Gln Gly Thr His Trp Pro Trp Thr Phe Gly Gln Gly Thr Lys
115 120 125

gtg gac atc aaa cga 399
Val Asp Ile Lys Arg
130

<210> 56
<211> 384
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(384)

<400> 56
atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc cca 48
Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

ggt gcc ata tgt gac att cag atg tcc cag tct cca tcc tcc ctg tct 96
Gly Ala Ile Cys Asp Ile Gln Met Ser Gln Ser Pro Ser Ser Leu Ser
20 25 30

gct tct gtg gga gac aga gtc acc atc acc tgc cgg gca agt cag ggc 144
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
35 40 45

ata act aat tat tta aac tgg tat cag cag aaa ccg ggg aaa gcc cct 192

Ile Thr Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

aac ctc ctg atc tat tat gca act cgt ttg gcg agc ggg gtc cca tca 240
Asn Leu Leu Ile Tyr Tyr Ala Thr Arg Leu Ala Ser Gly Val Pro Ser
65 70 75 80

agg ttc agc ggc agt gga tct ggg tcg gag tac agt ctc gcc atc agc 288
Arg Phe Ser Gly Ser Gly Ser Gly Ser Glu Tyr Ser Leu Ala Ile Ser
85 90 95

agc ctg cag cct gaa gat ttt gca acc tat ttc tgt caa cag ggt tat 336
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Tyr
100 105 110

agg gcc ccc tac act ttt ggc cag ggg acc aca gtg gag atc aaa cga 384
Arg Ala Pro Tyr Thr Phe Gly Gln Gly Thr Thr Val Glu Ile Lys Arg
115 120 125

<210> 57
<211> 390
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS
<222> (1)...(390)

<400> 57
atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

ctc cta ggt gcc aga tgt gac atc cag atg acc cag tct cct tct tcc 96
Leu Leu Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

ttg tct gca tct gta gga gac aga gtc acc atc act tgc caa gcc agt 144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser
35 40 45

cag ggt att agc aac tgg tta gcc tgg tat cag cag aaa ccg ggg aaa 192
Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

gcc cct aag ctc ctg atc tat gct gca tcc act ttc caa agt ggg gtc 240
Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Thr Phe Gln Ser Gly Val
65 70 75 80

cca tca agg ttc agc ggc agt gga tct ggg aca gag ttc act ctc acc 288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

atc agc agc ctg cag cct gaa gat ttt gca act tac tac tgt caa cag 336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

tat aat act tac cct ctc act ttc ggc gga ggg acc aag gtg gag atc 384
Tyr Asn Thr Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

aaa cga 390
Lys Arg
130

<210> 58
<211> 390
<212> DNA
<213> Macaca cynomolgus

<220>
<221> CDS

<222> (1)...(390)

<400> 58

atg gac ttg agg gcc ccc gct cat ctc cta ggg ctc ctg ctg ctc tgg 48
Met Asp Leu Arg Ala Pro Ala His Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

ctc cca ggt gcc aga ggt gac atc cag atg acc cag tct cca ccc tcc 96
Leu Pro Gly Ala Arg Gly Asp Ile Gln Met Thr Gln Ser Pro Pro Ser
20 25 30

ctg tct gcg tct gtt ggg gac act gtc agt ctt act tgt cgg gca agt 144
Leu Ser Ala Ser Val Gly Asp Thr Val Ser Leu Thr Cys Arg Ala Ser
35 40 45

cag cct att ggc agt aat tta aat tgg ttc cag caa aaa cct ggg agc 192
Gln Pro Ile Gly Ser Asn Leu Asn Trp Phe Gln Gln Lys Pro Gly Ser
50 55 60

ccc ccc aga ctc ctg atc tac ctt gcg acc gcc ttg caa cgt ggg atc 240
Pro Pro Arg Leu Leu Ile Tyr Leu Ala Thr Ala Leu Gln Arg Gly Ile
65 70 75 80

ccg tca agg ttt agc gcc act gga tct caa acc aat ttc act ctc acg 288
Pro Ser Arg Phe Ser Ala Thr Gly Ser Gln Thr Asn Phe Thr Leu Thr
85 90 95

atc acc ggc ctg cag cct gag gat ttc gca act tac ctc tgt ctg caa 336
Ile Thr Gly Leu Gln Pro Glu Asp Phe Ala Thr Tyr Leu Cys Leu Gln
100 105 110

cat act tct tac cca ttc act ttt ggc ccc ggg aca aag gtg gat atc 384
His Thr Ser Tyr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
115 120 125

aag cga 390
Lys Arg

130

<210> 59
<211> 88
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(56)
<223> CDRII

<400> 59
```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly
 1               5                  10                  15
Asp Thr Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asp Thr Glu
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Thr Leu Leu Ile
        35                  40                  45
Ser Asp Ala Ser Arg Leu Gln Thr Gly Val Ser Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Ile Ala Thr Tyr Tyr Cys
                85
```

<210> 60
<211> 94
<212> PRT
<213> Macaca cynomolgus

<220>

<221> DOMAIN
<222> (24)...(40)
<223> CDRI

<221> DOMAIN
<222> (56)...(62)
<223> CDRII

<400> 60

```
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1               5                  10                  15
Glu Arg Val Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45
Ala Pro Gln Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60
Pro Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80
Ile Ser Gly Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
                85                  90
```

<210> 61
<211> 93
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (24)...(39)
<223> CDRI

<221> DOMAIN
<222> (54)...(61)
<223> CDRII

<400> 61

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ile Pro Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30
Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Gln Pro
35 40 45
Pro Arg Leu Leu Ile Tyr Gln Val Ser Asn Arg His Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Thr Glu Asp Val Gly Val Tyr Ser Cys
85 90

<210> 62
<211> 88
<212> PRT
<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(56)
<223> CDRII

<400> 62
Asp Ile Gln Met Ser Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Thr Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45
Tyr Tyr Ala Thr Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Ser Glu Tyr Ser Leu Ala Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys

85

<210> 63

<211> 88

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(56)

<223> CDRII

<400> 63

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Gly Ile Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Phe Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys
85

<210> 64

<211> 88

<212> PRT

<213> Macaca cynomolgus

<220>
<221> DOMAIN
<222> (24)...(34)
<223> CDRI

<221> DOMAIN
<222> (50)...(56)
<223> CDRII

<400> 64

```
Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Thr Val Ser Leu Thr Cys Arg Ala Ser Gln Pro Ile Gly Ser Asn
            20                  25                  30
Leu Asn Trp Phe Gln Gln Lys Pro Gly Ser Pro Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Leu Ala Thr Ala Leu Gln Arg Gly Ile Pro Ser Arg Phe Ser Ala
    50                  55                  60
Thr Gly Ser Gln Thr Asn Phe Thr Leu Thr Ile Thr Gly Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Leu Cys
                85
```

<210> 65
<211> 360
<212> DNA
<213> Rat

<220>
<221> CDS
<222> (1)...(360)

<400> 65

```
gac acg gtg ctg acc cag tct cct gct ttg gct gtg cct cca gga gag       48
Asp Thr Val Leu Thr Gln Ser Pro Ala Leu Ala Val Pro Pro Gly Glu
 1               5                  10                  15
```

```
agg gtt acc gtc tcc tgt agg gcc agt gaa agt gtc agt aca ttt ttg       96
Arg Val Thr Val Ser Cys Arg Ala Ser Glu Ser Val Ser Thr Phe Leu
            20                  25                  30

cac tgg tat caa cag aaa cca gga cat caa ccc aaa ctc ctc atc tat      144
His Trp Tyr Gln Gln Lys Pro Gly His Gln Pro Lys Leu Leu Ile Tyr
        35                  40                  45

cta gcc tca aaa cta gaa tct ggg gtc cct gcc agg ttc agt ggc ggt      192
Leu Ala Ser Lys Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Gly
    50                  55                  60

ggg tct ggg aca gac ttc acc ctc acc att gat cct gtg gag gct gat      240
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu Ala Asp
65                  70                  75                  80

gac act gct acc tat tac tgt cag cag acc tgg aat gat cct cgg acg      288
Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Thr Trp Asn Asp Pro Arg Thr
                85                  90                  95

ttc ggt gga ggc acc aag ctg gaa ttg aaa cgg gct gat gct gca cca      336
Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
            100                 105                 110

act gta tct atc ttc cca cca tcc                                      360
Thr Val Ser Ile Phe Pro Pro Ser
        115                 120
```

<210> 66
<211> 360
<212> DNA
<213> Rat

<220>
<221> CDS
<222> (1)...(360)

<400> 66

gag gtc cag ctg cag cag tct gga cct gag gtt ggg agg cct ggg tcc 48
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Val Gly Arg Pro Gly Ser
1 5 10 15

tca gtc aag att tct tgc aag gct tct ggc tac acc ttt aca gat tac 96
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

gtt ttg aat tgg gtg aag cag agt cct gga cag gga ctg gaa tgg ata 144
Val Leu Asn Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

gga tgg att gat cct gac tat ggt act act gat tat gct gag aag ttc 192
Gly Trp Ile Asp Pro Asp Tyr Gly Thr Thr Asp Tyr Ala Glu Lys Phe
50 55 60

aaa aag aag gcc aca ctg act gca gat aca tcc tcc agc aca gcc tac 240
Lys Lys Lys Ala Thr Leu Thr Ala Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80

atc cag ctt agc agc ctg aca tct gag gac aca gcc acc tat ttt tgt 288
Ile Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

gct aga tct agg aat tac gga gga tat att aat tac tgg ggc caa gga 336
Ala Arg Ser Arg Asn Tyr Gly Gly Tyr Ile Asn Tyr Trp Gly Gln Gly
100 105 110

gtc atg gtc aca gtc tcc tca gct 360
Val Met Val Thr Val Ser Ser Ala
115 120

<210> 67
<211> 109

<212> PRT
<213> Pan troglodytes

<400> 67

Ala Val His Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15
Asp Ser Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Ile Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Phe Asp Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Arg Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Gly Trp Gly Thr His Pro
                85   90   95
Tyr Asn Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            100   105

<210> 68
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> rat/chimpanzee sequence

<400> 68

Asp Thr Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15
Asp Ser Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Ser Thr Phe
            20   25   30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Leu Ala Ser Lys Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Arg Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Trp Asn Asp Pro Arg

85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg

100 105

<210> 69

<211> 128

<212> PRT

<213> Pan troglodytes

<400> 69

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Phe

20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile

35 40 45

Ser Leu Val Ser Trp Asp Ser Tyr Asn Ile Tyr His Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Ser Leu Tyr

65 70 75 80

Leu Gln Met Asn Asp Leu Arg Pro Glu Asp Thr Ala Ile Tyr Phe Cys

85 90 95

Ala Lys Ala Asp Thr Gly Gly Asp Phe Asp Tyr Val Ser Asp Ser Trp

100 105 110

Arg Cys Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser

115 120 125

<210> 70

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> rat/chimpanzee sequence

<400> 70

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Val Leu Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Asp Tyr Gly Thr Thr Asp Tyr Ala Glu Lys Phe
50 55 60

Lys Lys Lys Ala Thr Leu Ser Ala Asp Thr Ser Arg Asn Ser Ala Tyr
65 70 75 80

Leu Gln Met Asn Asp Leu Arg Pro Glu Asp Thr Ala Ile Tyr Phe Cys
85 90 95

Ala Arg Ser Arg Asn Tyr Gly Gly Tyr Ile Asn Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser
115

<210> 71

<211> 354

<212> DNA

<213> Murine

<220>

<221> CDS

<222> (1)...(354)

<400> 71

caa gtt cag ctt caa cag tct gga gct gag ctg atg aag cct ggg gcc 48
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
1 5 10 15

tca gtg aag ata tcc tgc aag gct act ggc tac aca ttc agt agc tac 96
Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

tgg ata gag tgg gta aag cag agg cct gga cat ggc ctt gag tgg att 144

```
Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45

gga gag att tta cct aga agt ggt aat act aac tac aat gag aag ttc      192
Gly Glu Ile Leu Pro Arg Ser Gly Asn Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

aag ggc aag gcc aca ttc act gca gaa aca tcc tcc aac aca gcc tac      240
Lys Gly Lys Ala Thr Phe Thr Ala Glu Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

atg caa ctc agc agc ctg aca cct gag gac tct gcc gtc tat tac tgt      288
Met Gln Leu Ser Ser Leu Thr Pro Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

tca agt cgc ggc gtc agg ggc tct atg gac tac tgg ggt caa gga acc      336
Ser Ser Arg Gly Val Arg Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

tca gtc acc gtc tcc tca                                              354
Ser Val Thr Val Ser Ser
        115
```

<210> 72
<211> 324
<212> DNA
<213> Murine

<220>
<221> CDS
<222> (1)...(324)

<400> 72

```
gat att cag atg acc cag act aca tcc tcc ctg tct gcc tct ctg gga       48
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15
```

```
gac aga gtc acc atc act tgc agg tca agt cag gac att agc aat ttt       96
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asp Ile Ser Asn Phe
            20                  25                  30

tta aac tgg tat cag cag aaa cca gat gga act gtt aaa ctc ctg atc      144
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

tac tac aca tca aca tta cac tca gga gtc cca tca agg ttc agt ggc      192
Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

agt ggg tct gga aca gat tat tct ctc acc att agc aac ctg gag caa      240
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

gaa gat att gcc act tac ttt tgc caa cag ggt aat acg ctt cct tgg      288
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp
                85                  90                  95

acg ttc ggt gga ggc acc aac ctg gaa atc aaa cgg                      324
Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys Arg
            100                 105
```

<210> 73

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/chimpanzee sequence

<400> 73

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15
```

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asp Ile Ser Asn Phe
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 74

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/chimpanzee sequence

<400> 74

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
20 25 30

Trp Ile Glu Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Arg Ser Gly Asn Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Ser Phe Asn Ala Asp Thr Ser Thr Asn Ile Ala Tyr
65 70 75 80

Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Ser Arg Gly Val Arg Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser

115

<210> 75

<211> 360

<212> DNA

<213> Murine

<220>

<221> CDS

<222> (1)...(360)

<400> 75

```
caa gtt cag ctt caa cag cct ggg gct gag ctt gtg aag tct ggg gcc      48
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Ser Gly Ala
 1               5                  10                  15

tca gtg aag ctg tcc tgc aag gct tct ggc agt acc ttc acc agc tac      96
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr
            20                  25                  30

tgg atg cac tgg gtg aag cag agg cct gga cga ggc ctt gag tgg att     144
Trp Met His Trp Val Lys Gln Arg Pro Gly Arg Gly Leu Glu Trp Ile
        35                  40                  45

gga agg att gat cca aat agt ggt ggt act aag gat aat gag aag ttc     192
Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Asp Asn Glu Lys Phe
    50                  55                  60

aag agc aag gcc aca ctg act gta gac aaa ccc tcc agc aca gcc tac     240
Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Pro Ser Ser Thr Ala Tyr
65                  70                  75                  80

atg cag ctc agc agc ctg aca tct gag gac tct gcg gtc tat tat tgt     288
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

gca aga gag acc tac tat gat tcc tcg ttt gct tac tgg ggc caa ggg     336
```

Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
100 105 110

act ctg gtc act gtc tct gca gcc 360
Thr Leu Val Thr Val Ser Ala Ala
115 120

<210> 76
<211> 336
<212> DNA
<213> Murine

<220>
<221> CDS
<222> (1)...(336)

<400> 76
gat att gtt atg act cag tct caa aaa ttc atg tcc aca tca gta gga 48
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

gac agg gtc agc gtc acc tgc aag gcc agt cag aat gtg ggt act aat 96
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

gta gcc tgg tat caa cag aaa cca ggg caa tct cct aaa gca ctg att 144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

tac tcg gca tcc tac cgg tac agt gga gtc cct gat cgc ttc aca ggc 192
Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

agt gga tct ggg aca gat ttc act ctc acc atc agc aat gtg cag tct 240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

gaa gac ttg gca gag tat ttc tgt cag caa tat aac agc tat cct ctc 288
Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

acg ttc ggt gct ggg acc aag ctg gag ctg aaa cgg gct gat gct gca 336
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
100 105 110

<210> 77
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> murine/chimpanzee sequence

<400> 77
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
35 40 45
Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 78
<211> 118
<212> PRT

<213> Artificial Sequence

<220>
<223> murine/chimpanzee sequence

<400> 78

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Asp Asn Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Asn Val Asp Lys Ser Thr Asn Ile Ala Tyr
65 70 75 80

Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser
115

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Asp Asn Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ala
115

<210> 80

<211> 102

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/human sequence

<400> 80

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr
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<213> Pan troglodytes

<400> 81

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
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Trp Gly Arg Gly Ile Leu Val Ile Val Ser Ser
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<210> 86

<211> 11

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<213> Pan troglodytes

<400> 86

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
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<210> 87

<211> 11

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<400> 87

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
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<210> 88

<211> 11

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Trp Gly Arg Gly Val Leu Val Thr Val Ser Ser
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Trp Gly Gln Gly Val Gln Val Thr Val Ser Ser
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1 5 10

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1 5 10

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Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
1 5 10

<210> 97
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<213> Pan troglodytes

<400> 97

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09131

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 39/395
US CL :530/387.3; 424/133.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.3; 424/133.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Medline, Biosis
search terms: immunoglobulin, antibody, framework regions, CDR grafted, humanized, primatized

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANDERSON et al. A primatized MAb to Human CD4 causes receptor modulation without marked reduction in CD4+ T cells in Chimpanzees: In vitro and in vivo characterization of a MAb (IDEC-CE9.1) to human CD4. Clinical Immunology and Immunopathology. July 1997, Vol. 84, No. 1, pages 73-84, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
26 JULY 1999	18 AUG 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JULIE BURKE D. Lawrence For
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 20-31
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

the claim contain specific sequence identification numbers however the application has not complied with the sequence requirements.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.